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Cyclospora, *Eimeria*, *Isospora* and *Cryptosporidium* spp.

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CYCLOSPORA, EIMERIA, ISOSPORA, AND *CRYPTOSPORIDIUM* SPP.

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INTRODUCTION. Coccidia are exceptionally common protist parasites of both vertebrates and, to a lesser extent, invertebrates. Every vertebrate species that ever has been examined intensively, over a broad geographic range, has been found to have at least one coccidian species unique to it and may have as many as five, ten, or more species. They also may have additional coccidia shared with close relatives (congenerics, sometimes confamilials) and/or with sympatrics. The history of the development of our knowledge about coccidian parasites of wild mammals is long and tangled and has been reviewed by Levine (1973a,b), Joyner (1985), and Long and Joyner (1996). Suffice it to say that the coccidia were among the very first protozoans ever visualized when Antonie van Leeuwenhoek saw what surely were the oocysts of *Eimeria stiedai* in the bile of a rabbit in 1674 (see Wenyon 1926; Dobell 1932).

In this review, we limit our coverage to the coccidia of wild mammals that have direct (homoxenous) life cycles; reproduce both asexually (merogony) and sexually (gamogony) within the epithelial or endothelial cells of the gastrointestinal tract or related structures (e.g., bile duct, renal tubular epithelium, etc.) of their host; and produce as an end product, a resistant propagule, the oocyst, which leaves the host, usually via the feces. By far, the majority of coccidia with these characteristics are placed taxonomically into four genera contained in two families: Eimeriidae (*Cyclospora, Eimeria, Isospora*) and Cryptosporidiidae (*Cryptosporidium*). The taxonomy of the coccidia is reviewed below.

Before proceeding, we must distinguish between *infection* by coccidia and *coccidiosis.* Most wild mammals examined are found to be infected with coccidian parasites at one or more times during their life, and some (e.g, wild rabbits, some squirrels) may be infected during their entire lives with several species that constantly cycle through them. Given this ubiquitous nature of the coccidia, it is likely that most probably are harmless under natural, wild conditions. It is only when hosts are brought together in groups, enhancing transmission via their rapid, direct life cycles, that some species cause disease. As a result, coccidiosis is recognized as a major health hazard only during intensive husbandry of domestic animals, in wild animals that are in captivity (i.e., zoos, breeding or research facilities), in wild animal populations when habitat is lost and crowding occurs, or in wild animal species that have great reproductive potential and are protected by laws so that their populations increase inordinately (e.g., kangaroos in Australia); the latter two conditions are the result of human intervention or perturbation.

By searching the relevant literature, we can gain a sense of the prevalence of this disease (coccidiosis) in wild mammals. For those who study disease processes, one of the logical outlets to publish their findings is the *Journal of Wildlife Diseases,* which started publication in 1965. From 1965 to 1996, the *JournaL of Wildlife Diseases* published 2830 articles, abstracts, and case reports on wildlife diseases and > 50 lengthy articles as part of their microfiche series. During these 32 years, 27–117 articles were published each year (mean = 90 articles/year). In 5 years (1965, 1968, 1972, 1976, 1982) no articles appeared on coccidia, and in 7 addi-

tional years (1971, 1978, 1979, 1981, 1987, 1989, 1995) no articles mentioned coccidia in mammals; in all years, only 76 articles (2.7%) reported coccidia in wild animals, but only 39 (1.3%) covered topics dealing with mammalian infections with coccidia, 32 with *Eimeria* and *Isospora* spp., and 7 with *Cryptosporidium* spp.

Of the 32 articles addressing *Eimeria* and/or *Isospora* infections in mammals, 16 were simple surveys from bison (2), coyotes (2), deer (1), foxes (2), gophers (1), monkeys (1), mouflons (1), opossums (2), and rabbits (4); 9 were descriptions/redescriptions of oocysts; 4 documented experimental transmission of oocysts in deer (2), pigs (1), and squirrels (1); and only 3 reported pathological processes: 1 in wild rabbits (death during captivity, cause unknown), another in a camel (death in a zoo animal with clinical intestinal coccidiosis), and the third in two captive wombats (pathology demonstrated histologically during heavy infection in juvenile animals; one animal died, see below).

Of the seven articles that identified *Cryptosporidium* infections in deer, foxes, opossums (experimental infection), primates, raccoons, rabbits, rodents (voles), and ruminants, only Heuschele et al. (1986) suggested a cause and effect relationship between the presence of *Cryptosporidium* sp. and clinical disease (diarrhea) in 52 of 183 (28%) neonatal captive ruminants and in 2 of 86 (2%) captive primates. Thus, it seems clear that pathogenicity of coccidian parasites in wild mammals may be overestimated, and coccidiosis appears, in most cases, to be a disease due to human intervention.

CLASSIFICATION. The protistan phylum Apicomplexa Levine, 1970 comprises a large, heterogeneous assemblage of obligate, intracellular parasites consisting of five major groups: coccidia, gregarines haemogregarines, piroplasms, and malarial organisms. Members of this phylum are characterized further by having an apical complex typically composed of one or more polar rings, rhoptries, micronemes, and often a conoid. Subpellicular microtubules and micropores are also a common feature of this group. Three classes currently are recognized, based primarily on the presence and structure of a cone-shaped organelle, the conoid, located within the anterior end of one or more stages of the organism. The coccidia are placed in the class Conoidasida (Levine 1988), which is typified by the presence of a complete conoid consisting of a hollow, truncate cone.

The Conoidasida has two subclasses, Gregarinasina Dufour, 1828 and Coccidiasina Leukart, 1879. The gregarines are large, are generally homoxenous, and occur commonly in the digestive tract or body cavity of invertebrates or lower chordates; mature gamonts of most species are extracellular, with their apical ends often modified into attachment organelles called mucrons or epimerites. The coccidia have gamonts that usually develop intracellularly. A mucron or epimerite is lacking and, though some species are found in invertebrates, most tend to infect vertebrates. Life cycles may be either homoxenous or heteroxenous.

Four orders within the coccidia are distinguished by the presence or absence of various sexual and asexual stages. The order Eucoccidiorida (Léger and Duboscq 1910) is the largest, and members all possess merogony, gamogony, and sporogony. Suborders are recognized by the number of microgametes produced and whether or not gametes associate in syzygy prior to fertilization. The suborder Eimeriorina (Léger 1911) is typified by coccidia that lack syzygy, produce microgametocytes with many flagellated, motile microgametes, and possess a stationary rather than motile zygote. Two families, the Eimeriidae (Minchin 1903) and Cryptosporidiidae (Léger 1911), contain members that often parasitize enteric sites in mammals.

Eimeriids are homoxenous or facultatively heteroxenous, with merogony, gamogony, and formation of oocysts occurring within the same host. Oocysts leave the host via the feces and are unsporulated; sporogony occurs outside the host. The most speciose genus is *Eimeria* Schneider, 1875, which contains > 1700 named species. The genus *Isospora* Schneider, 1881 also is well represented with > 350 species. The genus *Cyclospora* Schneider, 1881 has fewer than 20 named species but has generated significant interest in recent years because at least 1 species appears to be a common parasite of humans. The three genera are distinguished by the structure of their sporulated oocysts: those of *Eimeria* spp. possess four sporocysts, each with two sporozoites (Fig. 16.8, c-c^1); those of *Cyclospora* possess two sporocysts, each with two sporozoites (Fig. 16.8, a-a^1); and those of *Isospora* spp. have two sporocysts, each with four sporozoites (Fig. 16.8, d-d^1).

Cryptosporidids contain a single genus, *Cryptosporidium.* All known species are homoxenous, and development occurs just under the host cell membrane rather than deep within it. Thus, the parasites appear, at first, to develop extracellularly on the lumenal surface of host cells. All developmental stages possess a unique feeder organelle, at the interface between parasite and host cell. This organelle appears to consist of a desmosome-like junction and ribosomal-studded foldings of the parasite cytoplasm. Their microgametes are unusual among coccidia because they lack flagella. Oocysts sporulate endogenously, but when sporulated, they lack sporocysts and contain four naked sporozoites (Fig. 16.8, b-b^1).

Since the oocyst is the stage that leaves the host, usually in the feces, it is the structure most readily available to the practitioner who wants to identify the coccidian species, in most cases without having to kill the host. Thus, about 98% of the coccidian species known from mammals are characterized only from this one life-cycle stage, the sporulated oocyst. Although Levine (1962) once calculated there could be at least 2,654,736 structurally different sporulated oocysts (and hence structurally different species) in the *Eimeria* alone, in reality it doesn't work that way. In some

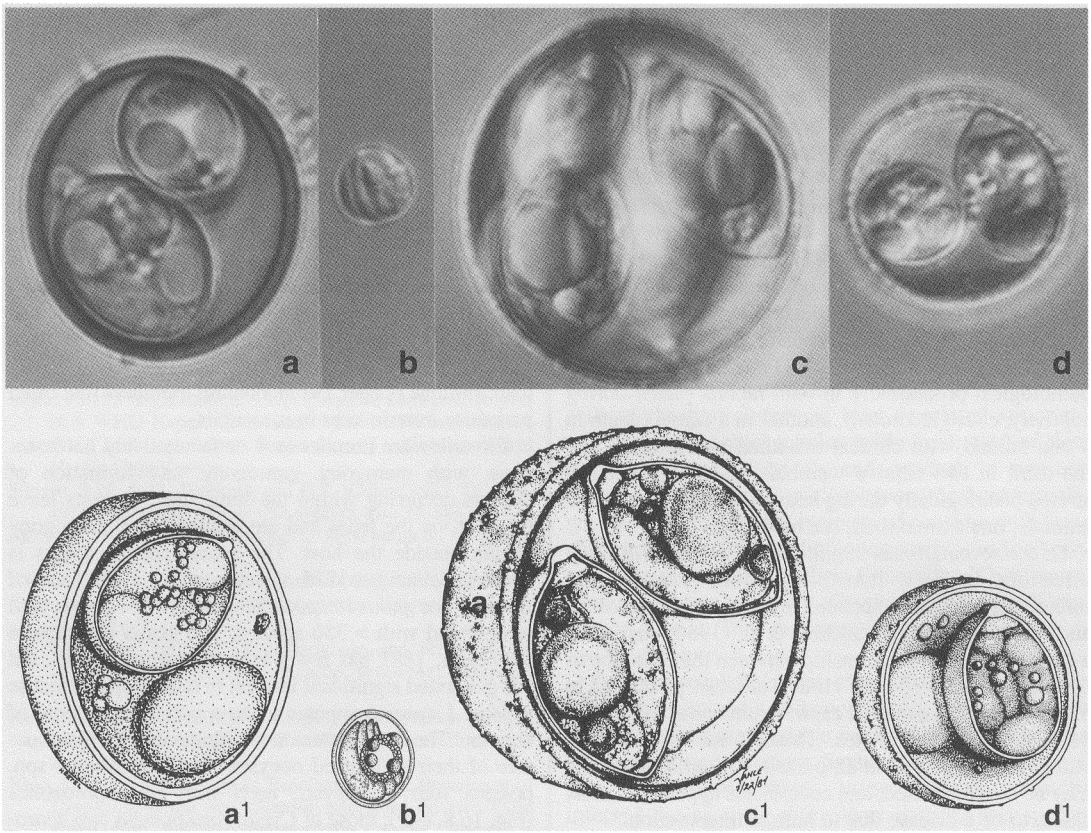

FIG. 16.8—Photomicrographs (a–d) and line drawings (a^1–d^1) of sporulated oocysts of the four genera discussed in this chapter. **(a, a^1)** *Cyclospora angimuriensis* Ford, Duszynski & McAllister, 1990 from *Chaetodipus hispidus*.**(b, b^1)** *Cryptosporidium parvum* Tyzzer, 1912 from humans. **(c, c^1)** *Eimeria parastiedica* Duszynski, 1985 from *Neurotrichus gibbsi.* **(d, d^1)** *Isospora brevicauda* Hertel & Duszynski, 1987 from *Blarina brevicauda.* Figures were chosen to show the variability in size and shape (*C. parvum,* for example, is ~7.0 (μm long) of oocysts within and between the two families of coccidia discussed in this chapter and some of the key structural features of sporulated oocysts noted in Figure 16.9 a–d.

cases, oocysts from unrelated host species look very nearly identical in size and structure and cannot be reliably differentiated by morphology and size alone (Joyner 1982). In other instances, a single coccidian species may produce oocysts that vary greatly in size (40%) and appearance (Duszynski 1971; Parker and Duszynski 1986; Gardner and Duszynski 1990). In truth, sporulated oocysts of *Eimeria, Isospora,* and *Cyclospora* have a limited number of structural characters, and those of *Cryptosporidium* even fewer. Unfortunately, the fewer the number of morphological characteristics, the more bothersome the species problem becomes, and within the Eimeriidae and Cryptosporidiidae, it is difficult to delimit what is a species to everyone's satisfaction. Thus, if the taxonomy of these groups is to be useful for higher level examination (systematic, phylogenetic, zoogeographic, host specificity, and other studies), the *taxonomic procedure* followed in collecting oocysts and documenting new species should be consistent and should follow the intent, if not the letter, of the International Code of Zoological Nomenclature (Ride et al. 1985); after all, the value of any classification scheme, from the species to all higher taxonomic categories, rests on the foundation of the species description.

Lom and Arthur (1989) recognized a serious deficiency in the way myxosporean species were described, and in an attempt to standardize the effort of workers in the field, they published "A Guideline for the Preparation of Species Descriptions in Myxosporea." They pointed out the many difficulties created for later workers by published descriptions of poor quality and emphasized that such practice, "ridicules taxonomic research in this group in the eyes of other parasitologists." Similarly, Duszynski and Wilber (1997) emphasized greater precision in the description of new coccidian species when only the sporulated oocyst was available and tried to set minimal guidelines for proper description of coccidian oocysts.

LABORATORY METHODS

Saving and Storing Oocysts. Oocysts must be kept properly to remain viable so that their structural integrity remains intact until they are studied. Oocysts from most mammalian hosts keep best when fresh feces are placed into 2%–2.5% aqueous (w/v) potassium dichromate ($K_2Cr_2O_7$) in a 1:5 ratio of feces to $K_2Cr_2O_7$ (by volume). In field collections, either snap-cap or screw-cap 16–25-ml vials work well, but one should not fill the vial all the way to the top; leave a layer of air between the top of the feces-dichromate mixture and the cap to allow the oocysts some atmospheric oxygen. Unfortunately, other solutions for feces [e.g., 2% (v/v) aqueous sulfuric acid (see Wash et al. 1985) or common laboratory fixatives for oocysts (see Duszynski and Gardner 1991)] are unsatisfactory either for keeping oocysts viable or for preserving them as types.

Handling and Processing Oocysts. Upon return to the laboratory, the fecal-dichromate mixture should be placed into a petri dish, the fecal pellets broken, and the fecal material spread out in the dish and covered (Duszynski and Conder 1977). The petri dishes generally should be maintained at room temperature (20°C–23° C) 7–10 days, which will allow any oocysts present to sporulate. It has been our experience that fecal-dichromate mixtures should not be refrigerated prior to the sporulation process as this seems to interfere with sporulation success. In most species, the mixture can be washed from the petri dish with clean 2% $K_2Cr_2O_7$ into a screw-cap jar (baby food jars work well) after ~7–10 days, then put into a standard refrigerator (4°C–7° C) until examination. Oocysts processed in this way can remain viable, or at least structurally intact, in the refrigerator 3–4 years for some species. However, it is probably best to study and document the structure of sporulated oocysts as soon as possible after they are sporulated.

Sporulated oocysts are best separated from the dichromate-fecal mixture by suspending an aliquot (1–3 ml) from the sample in 12–14 ml of modified Sheather's (Sheather 1923) sugar flotation solution (500 g sucrose, 350 ml tap water, 5 ml phenol) via centrifugation (5 minutes at 1500 rpm [= 225 *g*]). It is best to use only number 1, 18 mm^2, coverslips on top of the 15-ml centrifuge tubes (those with a smooth, beaded edge work best) as this reduces the surface area that needs to be scanned for oocysts. After centrifugation, lift the coverglass carefully from the centrifuge tube, place onto a glass slide, and set aside for 5–10 minutes; this allows the sugar along the edges of the coverglass to harden and minimizes movement of the oocysts during observation, measurement, and photography. The coverglass should be scanned systematically (100–400X) until oocysts are located. Measuring and detailing the structure of sporulated oocysts should always be done using an oil immersion objective (Neofluar and Nomarski optics are both useful). Apochromatic lenses are superior to achromats, and the higher the numerical aperture on the objective lens, the more accurate will be the measurements.

Species Differentiation. We suggest that those interested in making accurate identifications of oocysts found in the feces of wild mammals carefully follow the guidelines proposed by Duszynski and Wilber (1997). First, make sure that the host has been reliably identified and that as much ecological information as possible is noted. Whenever possible, deposit the actual host specimen from which the new species was described (= symbiotype; see Frey et al. 1992 and Brooks 1993) into an appropriate, accredited museum. Next, use only sporulated oocysts for mensural data, being careful to identify all of the quantitative and qualitative features of the oocysts and sporocysts (Fig. 16.9, a-d). Finally, be sure that the published manuscript includes at least one photomicrograph of a sporulated oocyst and the accredited museum accession number, in addition to the composite line drawing.

Those who describe new coccidian species based only on the structure of sporulated oocysts should be aware that at least some host groups (e.g., ground squirrels) have coccidia that are not always strictly host specific (Duszynski 1986; Wilber et al. 1998). In addition, many species (e.g., *E. nieschulzi, E. arizonensis*) occur naturally over large geographic ranges especially when hosts (e.g., *Rattus*) are introduced from continent to continent through human activities or when individuals in a specious host genus (e.g., *Peromyscus*) have contiguous ranges across a continent. Thus, finding oocysts in a new host species or new geographic locality may not be sufficient to warrant creation of a new species.

Archiving Oocysts and Host Specimens. The cornerstone of taxonomy is the type specimen, which is intended to be unchanging and objective, whereas the limits of the nominal species are recognized to be subjective and transient. The type specimen serves as the anchor for the name, and to some extent, it *is* the name (Mayr et al. 1953). Without the type specimen, some contend there is no "species." Coccidia present problems when it comes to collecting type specimens for two major reasons: (1) their endogenous stages are intracellular, transient, difficult to collect, and impossible to identify under field conditions; and (2) no standardized methods have been developed to permanently preserve oocysts. Unlike other parasites (arthropods, helminths) that stay on/in the host for lengthy periods and easily can be preserved and deposited into museums for later retrieval, coccidian oocysts preserve poorly (Duszynski and Gardner 1991). Thus, historically, those who have described new coccidian species have done so based on quantitative and qualitative observations of the oocyst, on the host species and its locality, and by using a drawing as the type specimen. Although it may seem obvious that drawings are cartoons subject to author interpretation, this tradition

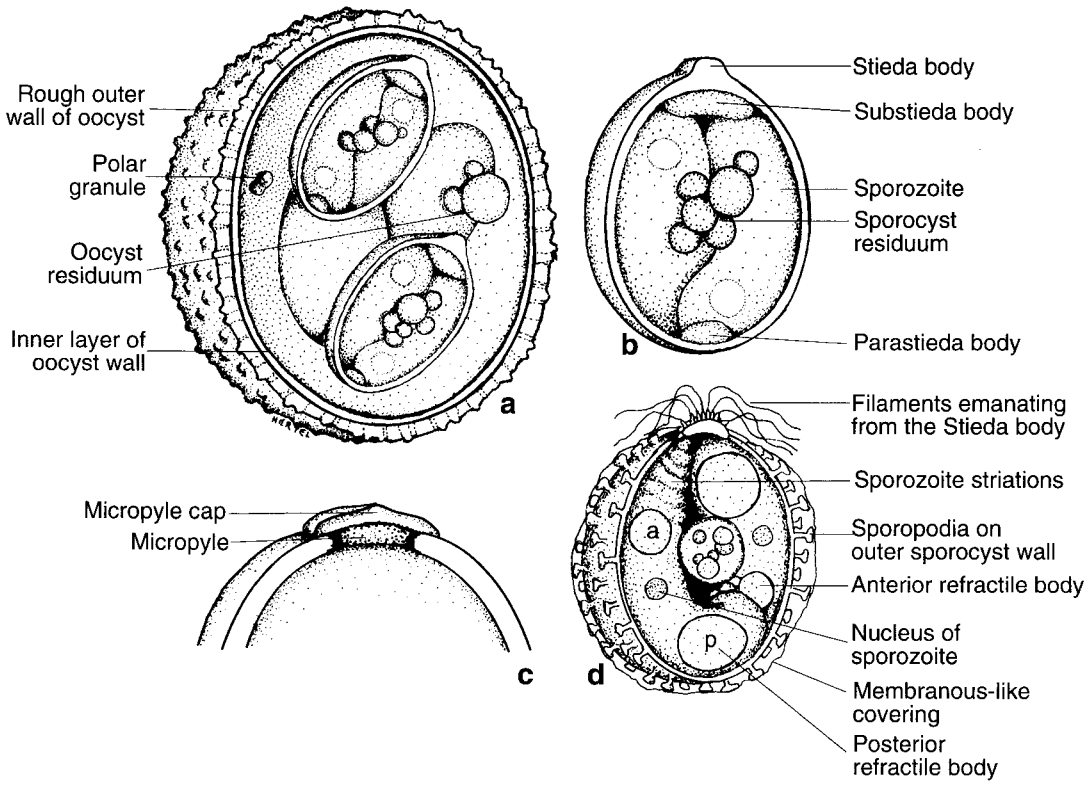

FIG. 16.9—Line drawings of the parts of (hypothetical) sporulated oocysts/sporocysts (*Cyclospora, Cryptosporidium, Eimeria, Isospora*). **(a)** A completely sporulated oocyst of an *Eimeria* sp. showing major structural features with four sporocysts, each with two sporozoites. **(b)** A sporulated sporocyst of an *Eimeria* sp. showing the major structural features, including two sporozoites. **(c)** The end of an oocyst showing micropyle and micropyle cap present in some oocysts, especially those of ruminants. **(d)** Another sporulated sporocyst showing a variety of structural features, some of which may be present on the sporocysts of different coccidia species.

among coccidian taxonomists has, unfortunately, persisted to the present. Bandoni and Duszynski (1988) criticized the lack of a type specimen tradition in coccidian systematic treatments and suggested that, at the very least, phototypes be deposited in accredited museums. The concept of phototypes, originally proposed by Kellerman (1912, see Frizzell 1933) was not new, but it has taken a long time for coccidian taxonomists to accept it.

Similarly, the traditional concept is that the coccidia are usually host specific. However, if one looks at many of the original descriptions of coccidia, the hosts are either haphazardly or incidently identified, some only by common names. This historical omission undermines the entire concept of host specificity. In an attempt to begin to correct the inadequacy of linking the name of a new coccidian species to an actual host species, Frey et al. (1992) suggested that parasitologists deposit specimens (symbiotypes) of hosts into museums from which type specimens of new parasite species are collected and identified. They correctly pointed out that whether one emphasizes microevolutionary (e.g., Price 1980) or macroevolutionary (e.g., Brooks and McLennan 1993) aspects of parasite evolutionary biology, much of the context of parasite evolution involves the hosts in which they live. Brooks (1993) extended the symbiotype concept by suggesting that parasitologists deposit voucher specimens of all host species examined in the course of survey or inventory studies, including purely ecological field studies. His argument, especially that documenting the case of our lack of knowledge about the parasites of "*Rana pipiens*," is compelling (no hosts deposited, numerous parasite species described, and now the host "species" is recognized as a clade of 27 or more extant and recently extinct species). Thus, the deposition of symbiotype host specimens into accredited museums is central to all parasitology if we are to develop a meaningful conceptual framework for our discipline.

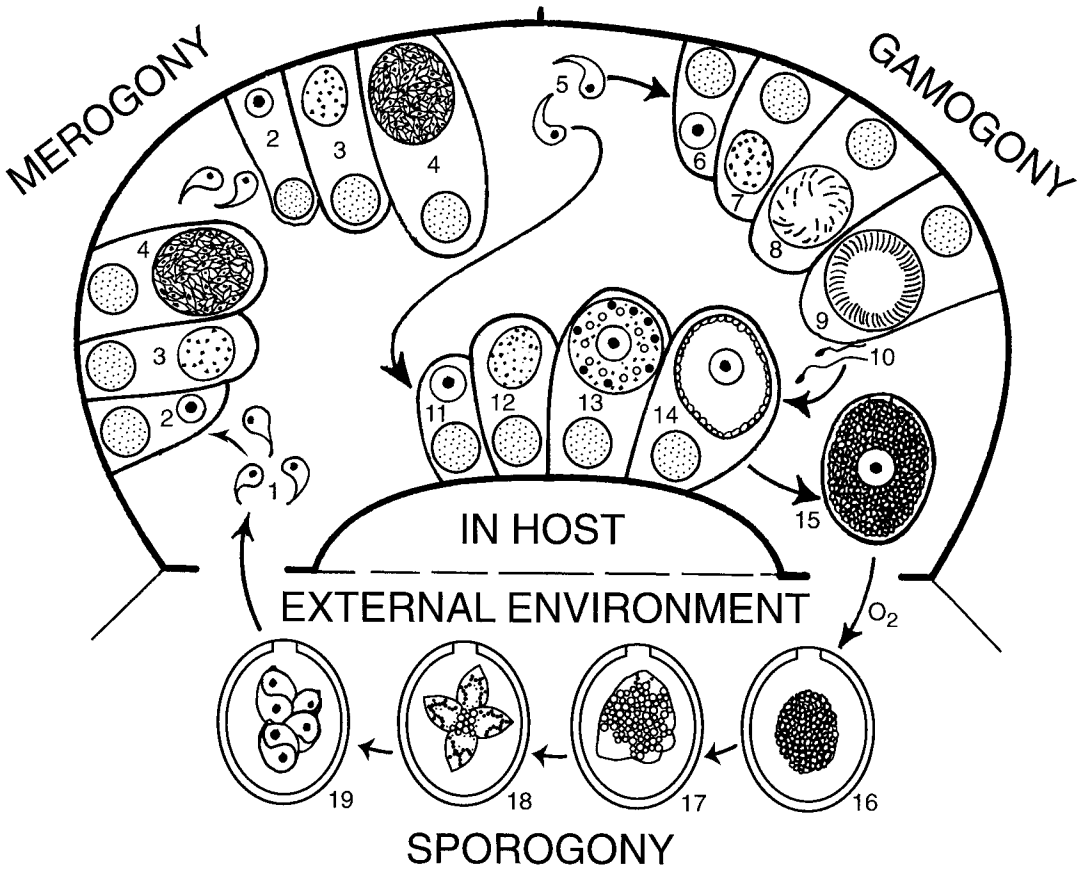

FIG. 16.10—Line drawing showing the major steps in the endogenous and exogenous development of a "typical" coccidia life cycle (*Cyclospora, Eimeria, Isospora;* somewhat modified in *Cryptosporidium,* see text and Fig. 16.11). **(1)** Sporozoites released from sporocysts/oocysts. **(2)** Sporozoite penetrates host enterocyte and rounds up. **(3)** Mitotic nuclear division in the meront. **(4)** Merozoite formation. **(5)** Last generation of merozoites penetrate other enterocytes to begin gamogony. **(6)** Merozoite rounds up in the first stage of developing into a microgametocyte. **(7)** Mitosis. **(8)** Microgametogenesis. **(9)** Mature microgametocyte with fully formed microgametes around the periphery. **(10)** Flagellated microgametes leave host enterocyte to penetrate another enterocyte with a fully developed macrogamete. **(11)** Merozoite rounds up in the first stage of developing into a macrogametocyte. **(12)** Early macrogamont. **(13)** Production of wall-forming bodies in the developing macrogamete. **(14)** Mature macrogamete. **(15)** After fertilization occurs and the 2N condition is restored, the unsporulated oocyst leaves the host enterocyte and enters the lumen of the gut. **(16)** Unsporulated oocyst, containing the sporoplasm of the next generation, leaves the host in the feces. **(17)** Meiosis takes place, and the sporocysts begin to form. **(18)** The pyramid stage of sporocyst development. **(19)** After the last mitotic division of the nuclei, sporozoite formation within each sporocyst is completed, resulting in the sporulated oocyst, the transmission propagule that is infective to the next host.

FAMILY EIMERIIDAE

Life History. Known life cycles of eimerian and isosporan species from mammals are all homoxenous and all go through three developmental stages: merogony (asexual)→gamogony (sexual)→sporogony (spore formation). The first two stages occur within the epithelial or endothelial cells of the gastrointestinal tract or related structures (e.g., bile duct) of the host. The end product of gamogony, which results from fertilization, is a resistant oocyst, the only stage in the cycle to leave the host, usually via the feces. The details of this developmental cycle follow (see Fig. 16.10).

SPORULATED OOCYST. When ingested by an appropriate host (Fig. 16.10, nos. 19–1), the sporozoites within the sporocysts within the oocyst must first excyst before infection can proceed. If the oocyst has a micropyle and micropyle cap, these structures are somehow altered and made permeable, presumably by digestive processes of the stomach and/or upper

digestive tract (Wang 1982). If the oocyst does not have a micropyle, then the oocyst wall must be breached or broken. This process has been documented in chickens, where the crop and ventriculus rupture oocysts and free sporocysts, but in mammals it apparently is a combination of digestive and proteolytic enzymes that accomplishes this task (Kheysin 1967). The key to excystation is getting the sporocysts into contact with pancreatic enzymes, trypsin, bile, and/or bile salts (Kheysin 1967; Wang 1982).

EXCYSTATION OF SPOROZOITES. The details of excystation from sporocysts have been studied in vitro, but only in relatively few species when compared to the total number of described species from mammals (Box et al. 1980; Duszynski et al. 1981). Sporozoites excyst from sporocysts by two distinctly different methods, each related to sporocyst structure (presence or absence of a Stieda body). In *Eimeria* and *Isospora* spp. with sporocysts and Stieda bodies, the Stieda body disappears when exposed to digestive enzymes, the sub-Stieda body, if present, either pops out of the sporocyst or is digested in situ, and the sporozoites exit the sporocyst through a hole created by dissolution of these structures. Those species that possess a sub-Stieda body all excyst quite rapidly, whereas those with only a Stieda body excyst more slowly (for reveiws see Speer and Duszynski 1975; Speer et al. 1976; Duszynski et al. 1977). In species in which the sporocyst lacks a Stieda body, the sporocyst wall consists of four curved plates; digestive enzymes act upon the junction between two apposing plates, causing collapse of the sporocyst during which sporozoites are released randomly (Speer et al. 1973, 1976; Box et al. 1980). This method of excystation has been seen in *Isospora* spp. from canids (Speer et al. 1973), felids (Duszynski and Speer 1976), and primates (Duszynski and File 1974; Duszynski and Speer 1976), as well as in *Toxoplasma gondii* from cats (Christie et al. 1978) and *Sarcocystis* sp. from birds (Box et al. 1980). Unfortunately, it is not yet known whether those *Eimeria* spp. with sporocysts that lack Stieda bodies excyst in a similar manner.

PENETRATION OF HOST CELLS. Once the sporozoites are free within the intestinal milieu (Fig. 16.10, no. 1) they must penetrate a host cell to continue development. This is where the organelles of the apical complex (rhoptries, conoid, micronemes, etc.) come into play. Host cell invasion involves a sequential series of complicated steps that include recognition of and attachment to host cell surface components, formation of a tight moving junction that progressively envelops the sporozoite, discharge of microneme and rhoptry contents to facilitate entry into the host cell, formation and maintenance of a parasitophorous vacuole membrane, resealing the host cell membrane, and exocytosis of dense granules (for reviews see Chobotar and Scholtyseck 1982; Doran 1982; Sam-Yellowe 1996). Once safely inside its parasitophorous vacuole within the host cell, the sporozoite is ready to initiate merogony (asexual multiple fission).

MEROGONY. Before beginning nuclear division, the sporozoite usually develops into a spheroid stage, the uninuclear meront (Fig. 16.10, no. 2). As the meront grows, its nucleus divides (Fig. 16.10, no. 3). Eventually, cytokinesis occurs, forming merozoites (Fig. 16.10, no. 4), the number of which corresponds to the number of nuclei in the mature meront. In some species, nuclear division occurs before the spheroid stage develops, and the multinucleate meront maintains its elongate, sporozoite-like shape (Chobotar and Scholtyseck 1982). As few as two or as many as 100,000 merozoites can be formed by each sporozoite, depending upon the species (Kheysin 1967). Once the merozoites are mature, they leave their host cell, killing it in the process. Each merozoite then seeks to penetrate a new epithelial cell within which to undergo another merogonous process (Fig. 16.10, repeat nos. 2-4). The general consensus is that each eimerian and isosporan species has a genetically programmed, specific number of merogonous generations characteristic for that species. For example, *Eimeria separata* from *Rattus* and *E. bovis* from *Bos* each have two merogonous generations (Roudabush 1937; Hammond et al. 1963), whereas *E. nieschulzi,* also from *Rattus,* and *E. utahensis* from *Dipodomys* have four merogonous stages (Marquardt 1966; Ernst and Chobotar 1978). Whatever the number, these developmental stages result in tremendous biological magnification of the parasite.

GAMOGONY. After a specific number of merogonous generations, the merozoites (Fig. 16.10, no. 5) that enter host cells develop not into additional meronts, but into gamonts. Most of the last generation merozoites develop into macrogametocytes (macrogamonts) to form uninucleate macrogametes (Fig. 16.10, nos. 11-14). The other last generation merozoites develop into microgametocytes, each of which will undergo multiple fission to produce many motile, biflagellated microgametes (Fig. 16.10, nos. 6-9). These leave the cells in which they developed (Fig. 16.10, no. 10) and seek out and penetrate cells that have a mature macrogamete within (Fig. 16.10, no. 14), and fertilization occurs. The regulatory mechanisms that control whether a merozoite will transform into a macro- or microgamont, the ability of microgametes to distinguish and select cells with developed macrogametes, and the actual fertilization process, which happens very quickly, are all areas that warrant further study.

UNSPORULATED OOCYST. As development continues, two types of wall-forming bodies develop within the cytoplasm of the macrogamont (Scholtyseck 1973). After fertilization, a delicate fertilization membrane is formed, and the wall-forming bodies migrate toward and then fuse with the surface membranes of the zygote (Kheysin 1967). Finally, a resistant oocyst wall composed of two to four layers is formed (Speer et al. 1979;

Duszynski et al. 1981), endogenous development is completed, and it is time for the oocyst to leave the host (Fig. 16.10, no. 15). In most *Eimeria* and *Isospora* spp., the oocysts are discharged from their host in an undeveloped (unsporulated) state (Fig. 16.10, no. 16). The time period between when the host first ingested a sporulated oocyst and when the first unsporulated oocysts leave the host in its feces is called the prepatent period. The length of time that oocysts are passed in the host's feces is termed the patent period. These time intervals vary greatly between coccidian species and are dependent, in part, on parasite genome, the size of the inoculating dose, the number of endogenous stages, depth within the tissues where gamogony and fertilization was initiated, concurrent infections with other parasites, host age, the immune and nutritional status of the host, and to some degree, biotic and abiotic environmental factors.

SPORULATION. Once outside the host, oxygen, temperature, moisture, and lack of direct exposure to ultraviolet (UV) radiation are key elements in the survival of the oocyst and its ability to sporulate (Fig. 16.10, nos. 16-19). The cellular material within the oocyst (zygote, 2N) is called the sporoplasm. It generally is agreed that the first nuclear division that occurs in the sporoplasm is meiotic (Fig. 16.10, no. 17) (Canning and Anwar 1968; Canning and Morgan 1975; Wang 1982) and that subsequent divisions leading to sporocyst and sporozoite formation are mitotic. As soon as the meiotic division is completed, a second (mitotic) division follows quickly to form four nuclei, at which time four protrusions often appear on the surface of the zygote. These protrusions transform into pyramid-shaped structures (Fig. 16.10, no. 18) that eventually become rounded to form smaller cyst structures, the sporocysts. A single mitotic division of the nucleus later occurs within each sporocyst, after which the cytoplasm divides into two sporozoites (Fig. 16.10, no. 19). The process described is for *Eimeria* spp.; *Cyclospora* spp. have two sporocysts with two sporozoites each, and *Isospora* spp. have two sporocysts, each with four sporozoites, and both undergo a process similar in principle. The sporozoites within the sporulated oocyst are the actual infective units, and most sporulated oocysts are resistant to environmental extremes and are immediately infective to the next hosts that chance to ingest them.

Finally, within the last two decades, we have learned that there may be another mode of transmission for members of these monoxenous genera. At least a few species of *Isospora* have been shown to use paratenic (transport) hosts (Frenkel and Dubey 1972; Dubey and Fayer 1976; Matsui 1991), and extraintestinal tissue stages have been shown experimentally to be able to transfer/transmit a successful infection in some mammalian *Eimeria* species (Mayberry et al. 1989; Mottalei et al. 1992). Sporozoites excyst from oocysts ingested by these paratenic hosts, infect cells in various places within the body, and become dormant. If the infected host is eaten by the appropriate predator, these dormant sporozoites become active, infect enterocytes of the predator, and initiate a typical coccidian life cycle.

Epizootiology. *Eimeria* and *Isospora* spp. are ubiquitous, found in all orders of mammals that have been sampled for them. Unfortunately, many parasite surveys of mammals have concentrated only on helminth and/or arthropod companions and largely have ignored the coccidia and other protista. Nonetheless, there are about 869 *Eimeria* spp. and about 132 *Isospora* spp. described from all mammals to date (Table 16.11). This must be only a fraction of the number of species that occur in mammals and clearly points to the urgent need for more work in this area, especially given the alarming rate of habitat destruction and species extinctions.

For the purpose of this chapter, we divide the class Mammalia into five groups: humans, domesticated mammals [e.g., cattle, camels, sheep, goats, horses, pigs, dogs, cats, lab animals (mice, guinea pigs, rats), lagomorphs (rabbits), mink, etc.], game mammals (e.g., deer, antelope, moose, elk, bighorn sheep), zoo mammals (mostly exotics), and wild mammals (all others); obviously, there is overlap among the latter four groups. Most of our knowledge about life cycles, pathology and clinical disease, physiology, biochemistry, cell culture, immunology, and drug therapy comes from work on the *Isospora* and *Eimeria* spp. that infect humans and domesticated mammals (e.g., Long 1982; Lindsay and Todd 1993), but these are not the purview of this series. Information about the other three groups (game mammals, other wild mammals, and zoo mammals) is germane to our discussion, and each is addressed briefly below.

Game mammals. Most game mammals are in two orders, Artiodactyla and Lagomorpha, and species in each group have both economic (food, clothing) and recreational (hunting) value. Unfortunately, with the exception of deer (Cervidae, 25 *Eimeria* spp.) and the chamois (*Rupicapra,* 6 *Eimeria* spp.), only the coccidia of domestic Artiodactyla (Table 16.11) have been studied extensively (Levine and Ivens 1986). The literature on game hosts consists almost entirely of surveys (e.g., Beaudoin et al. 1970; Penzhorn et al. 1994; Gõmez-Bautista et al. 1996), descriptions of new species (e.g., Inoue and Inura 1991; Hussein and Mohammed 1992; Wilber et al. 1996) or redescriptions of named species (e.g., Todd et al. 1967), and experimental infections, usually in young animals given artificially massive doses of sporulated oocysts (15–100 x 10^3) (Abbas and Post 1980; Conlogue and Foreyt 1984; Lindsay and Blagburn 1985). Only rarely is any pathology (usually mild to severe diarrhea) reported under natural conditions (McCully et al. 1970). However, we often keep herding species in semicaptive conditions (preserves, ranches); such conditions of limited habitat and crowding may lead to occasional case reports about outbreaks of coccidiosis (Hussein and Mohammed 1992), although sometimes they do not (Penzhorn et al. 1994).

There are 13 genera of lagomorphs, and 65 *Eimeria* and two *Isospora* spp. have been named from 10 of them (Table 16.11). This host-parasite association is unique in many ways. Surveys have shown that all species are infected with coccidia when examined; the prevalence of infection has been reported from as low as 4% (Soveri and Valtonen 1983) to as high as 100% (Duszynski and Marquardt 1969), and infected animals usually are infected with from two to nine species. A number of species, *Eimeria intestinalis, E. piriformis, E. coecicola* (intestinal forms), *E. stiedai* (liver, bile duct), and a few others, are known to be highly pathogenic (Kheysin 1947, 1948; Pellérdy and Dürr 1970; Coudert et al. 1993), but these are found primarily in the Old World rabbit (*Oryctolagus cuniculus*). The 3 lagomorph genera from which 70% of their coccidia species are described are *Lepus, Oryctolagus,* and *Sylvilagus* (Levine and Ivens 1972, D.W. Duszynski, unpublished data). Although numerous surveys for coccidia and helminth parasites have been done on species in these genera, Andrews and Davidson (1980) noted a lack of salient coccidiosis lesions in conjunction with an absence of any cases of clinical coccidiosis in numerous surveys of wild rabbits. This suggested to them "that the pathogenicity of coccidian parasites in wild cottontails has been overestimated." Although some of the *Eimeria* that infect these genera have been shown by cross-infection experiments to be species specific (e.g., *E. sculpta:* see Carvalho 1943) other species (e.g., *E. neoleporis:* see Carvalho 1942, 1944; *E. stiedai:* Jankiewicz 1941) can be transmitted between genera. Other interesting work has been done with rabbit coccidia that has biological implications beyond the individual organisms used. Licois et al. (1990) were able to develop a precocious line of *E. intestinalis* by selection for early developmental oocysts after six consecutive passages in rabbits (*Oryctolagus*); more recently, Pakandl et al. (1996), developed a precocious strain of *E. media.* Such studies may lead to the development of immunity via attenuated pathogenicity in highly pathogenic strains (see Jeffers 1975; McDonald et al. 1986). Aly (1993) was able to infect dexamethaxone-treated mice with *E. stiedai* and achieve a patent infection in 20 of 25 mice; the prepatent period was 30–35 days, and patency lasted at least until 60 days postinfection. Perhaps host transfer occurs more often than we know under natural conditions where many random cross-transmission events must occur daily among syntopic hosts, especially those that have similar nutritional requirements and can provide coccidia with intestinal milieus similar to one another. Finally, molecular tools have begun to be used for diagnosis of coccidia species in veterinary parasitology (for review see Comes et al. 1996). Among the first to demonstrate this use with mammalian coccidia were Cere et al. (1995) who studied inter- and intraspecific variation of *Eimeria* spp. in rabbits using random amplified polymorphic DNA (RAPD) assays. Although profiles differed significantly among nine eimerian species, species-specific fingerprints were obtained that might prove useful in species diagnosis.

Other wild mammals. The major orders (numbers of species) of other wild mammals include rodents (Rodentia, 2015 spp.), bats (Chiroptera, 925 spp.), moles and shrews (Insectivora, 428 spp.), marsupials (orders Dasyuromorphia, Didelphiomorphia, Diprodontia, Microbiotheria, Notoryctemorphia, Paucituberculata, Peramelemorphia, 272 spp.), carnivores (Carnivora, 271 spp.), and primates (Primates, 233 spp.) (Table 16.11). The final order we will mention (Cetacea, 78 spp.) includes the world's largest and most endangered species.

When most people think about wild mammals, they generally do not think about rodents, which comprise the most specious order of mammals. Yet we know more about the coccidia of rodents than we do about those of any other mammalian order (Table 16.11). Levine and Ivens (1965) published the first comprehensive review on the coccidian parasites from rodents, a treatise they later revised and updated (1990). Their first review (1965) included 204 *Eimeria* and 10 *Isospora* spp., and their second (1990) listed 374 *Eimeria* and 39 *Isospora* spp., an increase of 199 described (named) species (93%) in 25 years (note their addendum). Even with this "plethora" of species, there remains an enormous void in our knowledge. To wit: (a) an additional 32 *Eimeria* and *Isospora* spp. are listed in Levine and Ivens (1990) without complete names because information is insufficient to justify species names; (b) < 15% of all 2015 rodent species (Wilson and Reeder 1993) have been examined for coccidia, and it is most likely that those named coccidia do not include all the coccidia species to be found in each host species; (c) most of the descriptions of sporulated oocysts are far from complete; (d) the complete life cycles of < 10 named species are known, and even the general location of endogenous development in the host is known for < 20% of the named species; (e) information about the molecular genetics (*e.g.,* gene sequences) is virtually nonexistent. Clearly, this is an area that deserves enormous research effort in the future.

Bats are the second most diverse order of mammals with > 900 species (Table 16.11). Surprisingly, however, there are only 30 valid *Eimeria* spp. described from bats worldwide (Duszynski 1997; Scott and Duszynski 1997; D.W. Duszynski, unpublished data) in comparison to > 400 eimerians described from rodents [Levine and Ivens (1990) listed 372]. Ubelaker et al. (1977) suggested that this low diversity of *Eimeria* in bats is due primarily to a lack of searching for them when bats are surveyed for parasites. However, examination of additional bats for coccidia by several authors since 1977 suggests that their overall prevalence is generally lower in bats than in rodents. Marinkelle (1968) found only 2 of 400 bats (< 1%) infected, and Scott and Duszynski (1997) found 28 of 548 (5%) infected with *Eimeria* spp. However, Yang-Xian and Fu-Qiang

(1983) reported 105 of 151 (70%) infected, so the prevalence of coccidia in bat species also can be quite variable. The factors that contribute to the prevalence of coccidia in vertebrates include, but are not limited to, host specificity, acquired immunity, and several abiotic factors (Marquardt et al. 1960; Todd and Hammond 1968a,b; Wilber et al. 1994a,b). Although no one has demonstrated it empirically, the abiotic factors most likely to contribute to the infection of bats by coccidia are the stability of the roost microclimate (e.g., relative humidity, temperature) and roosting behavior by bats (i.e., colonial vs. solitary). For example, bats that prefer crowded roosts with stable microclimates (e.g., maternity colonies in attics, caves) may be more likely to ingest sporulated oocysts than bats that prefer to roost alone where microclimates may be highly variable (e.g., trees, leaf litter). Compact roost types (attics, crevices) may bring bats into contact with feces more often than large, open roosts (caves). Also, increased grooming (maternity colonies) may contribute to a greater chance of bats ingesting infective oocysts (Scott and Duszynski 1997). No *Isospora* spp. have been found in bats, and all infected bats found to date have been infected only with a single species; no multiple species infections have been recorded. Finally, Gruber et al. (1996) recently examined 14 bats belonging to six different insectivorous species, and 4 bats, each a different species (*Pipistrellus pipistrellus, Myotis mystacinus, M. nattereeri,* and *Nyctalus noctula*), had renal coccidiosis with cystic tubular dilatation. Previously, Kusewitt et al. (1977) reported *Klossiella* sp. in the kidneys of two *Myotis sodalis.* However, the asexual and sexual developmental stages shown in the tubular epithelium and lumina and a "suggested unsporulated oocyst" demonstrated in a collecting duct were typical of *Eimeria* or *Isospora* infections (Eimeriidae), which look quite different than those of *Klossiella* (Klossiellidae). But since no sporulated oocysts were available for study, the genus of this coccidian organism is unknown. Most of those who have studied bats for coccidia have looked for oocysts only in bat feces. The possibility exists that many more coccidian species may have been found if the kidneys and urine also had been examined.

The insectivores have been described as a zoological catchall into which a number of ancient and seemingly distantly related taxa have been placed. Some insectivores are considered to be pests (e.g., moles on golf courses), while others (e.g., shrews) are important in human agriculture in the control of insect, slug and snail pests. Only about 8.6% (37/428) of insectivore species have been examined for coccidia, but these have produced a wealth of named species including about 48 *Eimeria,* 22 *Isospora,* and 5 *Cyclospora* spp. (Table 16.11); this is a significant increase in the number of species (24, 10, and 2, respectively) since Levine and Ivens (1979) last reviewed the coccidia of insectivores. The vast majority of these species are known only from the description of sporulated oocysts that have been studied in fecal samples from their hosts (e.g., Duszynski 1989; Duszynski and Upton 2000). A few of the endogenous stages of *Cyclospora caryolytica, C. talpae,* and *Eimeria goussevi* (Pellérdy and Tanyi 1968; Entzeroth and Scholtyseck 1984) from the European mole (*Talpa europaea*) and of *E. darjeelingensis, E. murinus,* and *E. suncus* (Ahluwalia et al. 1979; Sinha and Sinha 1980; Bandyopadhyay and Dasgupta 1985) from the house shrew (*Suncus murinus*) have been documented. To our knowledge, however, there are no complete life cycles known. This is certainly an area ripe for future study, especially given the interesting observation of Cable and Conway (1953) discussing endogenous stages of a coccidian parasite in the mammary tissues of a shrew.

The marsupials now occupy seven orders in the newest systematic treatise on mammals (Wilson and Reeder 1993), but only two orders have coccidia described from them. By far, the great majority of species live in Australia; most are herbivores, but a few are predators. To date, 56 *Eimeria* and only 2 *Isospora* spp. have been recorded from sporulated oocysts (Table 16.11). Of these, details of gamogony have been recorded for 4 *Eimeria* spp., only a few merogonous stages have been seen, and no complete life cycles are known. Beveridge (1993) reported that coccidiosis was a major disease of large kangaroos, but that continuous, simultaneous infection with several species of *Eimeria* make it impossible to determine which of the species present is the major pathogen. The eastern gray kangaroo (*Macropus giganteus*) seems to be particularly susceptible to developing pathology, and *E. wilcanniensis* (syn. *E. kogoni*) is thought to be the major pathogen. Barker et al. (1979) documented obvious intestinal tissue pathology due to *Eimeria arundeli* in wombats (*Vombatus ursinus*), and Beveridge (1993) mentioned that coccidia present in the echidna (*Tachyglossus aculetaus*) appear to cause a mild enteritis. However, coccidia found in many Australian marsupials (e.g., platypus, *Ornithorhynchus anainus*) either cause no obvious pathology or have not been formally described, or both (Beveridge 1993). For example, Beveridge (1993) reported that an undescribed *Eimeria* sp. was totally nonpathogenic in the bush-tailed opossum (*Trichosurus vulpecula*).

Levine and Ivens (1981) reviewed the coccidia [including *Besnoitia, Frenkelia, Sarcocystis,* and *Toxoplasma* (Sarcocystidae), which we do not cover] of carnivores and listed 78 named species of *Eimeria* (39) and *Isospora* (39) in 46 host species in 26 genera (7 families); these names included at least one *nomen nudum* and many species of questionable validity [e.g., 5 *Eimeria* spp. from *Felis* and 3 from *Leo* may be pseudoparasites; also see Arther and Post (1977), for pseudoparasites in *Canis*]. Wilson and Reeder (1993) lump the former mammalian order Pinnipedia (seals, sea cows) within the Carnivora (canids, felids, bears, raccoons, mustelids, etc.). Even 15 years after Levine and Ivens (1981), only 20% (55/271) of the carnivore species have been examined for coccidia, and about 107 species have been named (many of dubious

distinction), divided evenly between *Eimeria* and *Isospora* spp. (Table 16.11). The coccidia of domesticated *Canis* and *Felis* spp. were reviewed recently (Lindsay and Todd 1993; Lindsay et al. 1997a), and because of their importance to humans as companion animals it is their coccidia about which we have the most knowledge concerning life cycles, immunity, cross-transmission, and similar matters. Despite a few erroneous reports to the contrary, neither dogs nor cats (Lindsay and Todd 1993; Lindsay et al. 1997a) serve as hosts for *Eimeria* spp.; as far as is known, only *Isospora* spp. parasitize these hosts. In addition, both genera develop solid immunity following primary infection, and cross-infection work, to date, suggests that cats and dogs do not share their *Isospora* spp. Within the Canidae, however, cross-transmission can bridge generic boundaries; Bledsoe (1976), for example, demonstrated that *Isospora vulpina* from the silver fox (*Vulpes vulpes*) could be transmitted to beagle dogs (*Canis familiaris*). Within other Carnivora families and/or genera, only oocyst descriptions are known for the majority of reported species (many of these are questionable), with two exceptions. Within the Mustelidae, enteric (Blankenship-Paris et al. 1993), respiratory and urinary (Jolley et al. 1994), and biliary (Williams 1996) coccidiosis have been documented histologically in ferrets (*Mustela* spp.); and in the Phocidae, endogenous development of *Eimeria phocae* was reported in both asymptomatic and clinically ill harbor seals (*Phoca vitulina*) (McClelland 1993).

The most accepted taxonomic scheme divides the primates into two suborders, Prosimii (the lower primates) and the Anthropoidea (higher primates) (Nowak 1991); there are 7 *Eimeria* (natural) and 1 *Isospora* (experimental) spp. described from the former and 7 *Isospora* and 1 *Cyclospora* spp. from the latter (Duszynski et al. 1999). Lindsay and Todd (1993) and Lindsay et al. (1997a) recently reviewed the *Isospora* spp. from the higher primates. Only four valid species are known from wild, higher primates (excluding humans which have *Isospora belli* and two questionable species, *I. chilensis* and *I. natalensis*): *I. arctopitheci, I. callimico, I. endocallimici,* and *I. saimirae;* the latter three species are known only from the structure of their sporulated oocysts. Hsu and Melby (1974) described *I. callimico* from the feces of captive Goeldi's marmoset (*Callimico goeldi*) at a primate facility in Baltimore, Maryland. At almost the same time, *Isospora endocallimici* was described from five captive *C. goeldii* at the Tulane University Delta Regional Primate Research Center, Covington, Louisiana (Duszynski and File 1974). Two of these animals were born at the Center, the other three were born in the wild and imported from Peru. All animals were passing oocysts when examined, so it was not possible to state in which one(s) the infection originated. *Isospora saimirae* was described from the feces of a squirrel monkey, *Saimiri sciureus,* from Tocantins Island, Pará State, Brazil (Lainson and Shaw 1989). Ironically, the type locality now lies beneath the Tucurui Reservoir, a man-made lake built shortly after 1989. There are other isosporan species that have been named based on the structure of sporulated oocysts found in the feces of higher primates (e.g., *Isospora cebi, Isospora paponis*), but careful analysis (see Lindsay et al. 1997a) suggests these are likely oocysts of *Sarcocystis* spp. Finally, *I. arctopitheci* was described by Rodhain (1933) from a captive marmoset (*Callithrix penicillata*) that had died in France. He saw no connection between the presence of the parasite and death of the marmoset. *Isospora arctopitheci* is the most studied of the higher primate species. It has a broad host range, having been transmitted to members of six genera of New World primates, four families of carnivores and one marsupial species (according to Hendricks 1977). Its life cycle was described by Olcott et al. (1982) and is unusual in that asexual reproduction takes place by a process called endodyogeny rather than by merogony. In heavy experimental infections ($1–2 \times 10^5$ oocysts), 4 of 13 experimental titi marmosets (*Saguinus geoffroyi*) died 3 to 5 days after inoculation (Olcott et al. 1982). In all other reports of *Isospora* spp. from higher primates, infections do not show clinical symptoms under normal circumstances.

Finally, it is of interest that there are 7 *Eimeria* spp. described from lower primates, but only 1 *Isospora* sp. (experimentally). In general, our knowledge of primate coccidia is poor: *Eimeria, Isospora,* and *Cyclospora* spp. have been reported from 7 of 13 (54%) of the families (listed in Wilson and Reeder 1993), but only from 14 (23%) of the 60 genera and 18 (8%) of the 233 species (see Duszynski et al. 1999).

There are no coccidia described from cetaceans (whales); however, this is not because no one has looked. Dailey and Vogelbein (1991) published a parasite survey on 176 whales, including 35 sei whales (*Balaenoptera borealis* Lesson, 1828), 106 minke whales (*B. acutorostrata* Lacépede, 1804) and 35 sperm whales (*Physeter catodon* L., 1758). We examined the feces of these and about a dozen other cetaceans (D.W. Duszynski, unpublished), but were unable to find any structures resembling coccidian oocysts. Recently, Kuttin and Kaller (1996) described a species they named *Cystoisospora delphini* as the cause of enteritis in a captive bottle-nosed dolphin (*Tursiops truncatus*) at the Laboratory for Marine Mammals Research, Tel-Aviv University, Israel. They placed the oocysts of the organism they saw in the genus *Cystoisospora* because they believed that the dolphin, which had been in captivity 5 years, acquired the infection from (frozen, whole) fish it had been fed, but they did not present evidence of parasitic cysts in the presumed intermediate hosts. We believe that *Cystoisospora* is best considered a junior synonym of *Isospora.*

Zoo mammals. There is an increased interest in the diseases of zoo/captive animals worldwide (Fowler 1978, 1986, 1996a,b; Modl et al. 1995; Artois et al. 1996; Cubas 1996; Porter 1996; Schultz et al. 1996; Williams and Thorne 1996). Most mammals in zoos are

TABLE 16.11—The number of mammalian orders and species (Wilson and Reeder, 1993) showing the approximate number of host species that have coccidia described from them and the approximate numbers of *Eimeria, Isospora,* and *Cyclospora* spp. described from each order.

Order (Common Names)	No. of spp.	No. Host spp. with Coccidia	No. of spp. *Eimeria*	No. of spp. *Isospora*	No. of spp. *Cyclospora*
Artiodactyla (pigs, deer, sheep)	220	54	170	7	0
Carnivora (cats, dogs, seals)	271	55	56	51	0
Cetacea (whales, dolphins)	78	0	0	0	0
Chiroptera (bats)	925	26	30	0	0
Dasyuromorphia (Tasmanian devil)	63	0	0	0	0
Dermoptera (flying lemurs)	2	0	0	0	0
Didelphimorpha (American opossums)	63	6	6	2	0
Diprodontia (koala, kangaroos)	117	35	50	0	0
Hyracoidea (hyraxes)	6	0	0	0	0
Insectivora (shrews, moles)	428	37	48	22	5
Lagamorpha (rabbits, hares)	80	20	65	2	0
Macroscelidae (elephant shrews)	15	0	0	0	0
Microbiotheria (Monito del Monte)	1	0	0	0	0
Monotremata (spiny anteaters)	3	2	1	0	0
Notoryctemorphia (marsupial moles)	2	0	0	0	0
Paucituberculata (shrew opossums)	5	0	0	0	0
Peramelemorphia (bandicoots)	21	0	0	0	0
Perissodactyla (horses, zebras)	18	5	3	0	0
Pholidota (scaly anteaters)	7	1	1	0	0
Primates (monkeys, humans)	233	18	7	8	1
Proboscidea (elephants)	2	0	0	0	0
Rodentia (mice, rats, squirrels)	2015	280	415	40	1
Scadentia (tree shrews)	19	4	4	0	0
Sirenia (manatees, dugongs)	5	3	3	0	0
Tubulidentata (aardvarks)	1	0	0	0	0
Xenarthra (armadillos)	29	10	10	0	0
26	4629	556	869	132	7

large, exotic wild mammals. They present unique problems to zoo managers, veterinarians, and biologists alike for many reasons: (a) it is impossible to reproduce the abiotic environmental conditions of their native habitat (e.g., photoperiod, temperature and humidity extremes, space requirements); (b) it is impossible to duplicate the biotic conditions or interactions of their natural environment (e.g., seasonal dietary needs, coevolved invertebrates and vertebrates); (c) the presence of nonnative cohorts of other captive animals, crowding, and proximity of large numbers of people are "unnatural" and likely produce various levels of stress; (d) stress likely predisposes zoo mammals to parasitic diseases, especially those, like coccidia, with direct life cycles that do not require specialized intermediate hosts; and (e) captive/zoo animals have the potential to act as vectors of zoonoses. In addition, the concentration of like or nearly like mammals into small areas and

the ability of parasites with direct life cycles to greatly increase the number of transmission propagules via asexual reproduction, combined with the above factors, create conditions ideal for serious disease consequences due to parasites in zoo mammals and/or their keepers. Such disease manifestations may occur often, but they are seldom reported (e.g., Schillhorn van Veen 1986) or, if reported, often are not attributed to coccidian parasites. Sometimes, new species of coccidia are described from zoo mammals (e.g. Rastegaãeff 1930; Yakimoff and Matschoulsky 1940; Agrawal et al. 1981; Flach et al. 1991), but these reports must be interpreted with caution, given the conditions unique to zoos (above).

PREVALENCE IN WILD MAMMALS. Using the clear definitions given by Margolis et al. (1982), the prevalence (number hosts infected/number individuals examined) of coccidial infection in a given population of wild mammals may vary from 0% (e.g., bats) to 100% (e.g., cottontail rabbits), whereas the incidence (number new cases of infection/number uninfected individuals in the population) of infection usually is impossible to determine in feral mammal populations. Likewise, terms like intensity, density, abundance, and infrapopulation that are applicable to helminth infections have no meaning in coccidial infections. Even when one samples a large, representative number of individuals in a natural population, the prevalence determined is only a guess of the real prevalence of that coccidian species in the population. The reason(s) have to do with the transient nature of the coccidian infection. Suppose you sample an animal and no oocysts are found in its feces; that animal is considered negative for coccidia. However, it may be infected with one or more coccidia that are only in an asexual reproductive phase (merogony), not yet making oocysts or, because gamogony, fertilization, and oocyst discharge are relatively rapid events in most cycles, the last oocysts in the cycle may have been in the animal's fecal discharge just prior to its collection. Also, the first and last days of patency may have so few oocysts in the feces that they can be missed in routine fecal examinations, especially if the oocysts are small (< 10 μm). Other biotic (size of the infecting dose; age, nutritional, and immune status of the host; location where the feces are deposited) and abiotic (season, temperature, moisture, altitude, direct UV radiation, longitude) factors all influence the real incidence of coccidial parasites in a host population. Sometimes, less obvious environmental factors such as radon-rich soils may have a significant effect on both the prevalence and the survival of a coccidian parasite in its natural host population (Wilber et al. 1994b). Finally, repeated removal of host animals from a site will cause immigration rates high enough to mask or alter previous patterns of prevalence (Wilber and Patrick 1997). Thus, determining the true prevalence of coccidial infection in populations of wild mammals is tricky and inaccurate, at best.

SURVIVAL OF OOCYSTS. This is an area that deserves future, critical study, because most of what we know has been observed in the laboratory working with four species of chicken and two species of rabbit coccidia. Although we know that temperature, moisture and direct exposure to UV radiation (sunlight) all have an influence on the ability of oocysts to sporulate once discharged from the host to the external environment, the importance of these, and perhaps other, factors (e.g., mechanical vectors) and their interactions have not been precisely determined. In general, oocysts sporulate more slowly at lower temperatures and faster at higher temperatures (Becker and Crouch 1931; Edgar 1954). If maintained in an aqueous medium at < 10° C or > 50° C, oocysts will degenerate and die (Becker and Crouch 1931). Between these extremes, the percent of oocysts that will sporulate in a field-collected sample depends on the species, the time between collection and getting the sample to the laboratory, the temperature at which the sample was kept during that time (D.W. Duszynski, unpublished), the medium in which the fecal sample was stored (Duszynski and Wilber 1997), the rate of putrification of the sample, the amount of molecular oxygen available to the stored oocysts (Duszynski and Conder 1977), and possibly other factors such as the proximity of other, sporulating oocysts (Duszynski and Conder 1977). Once a field-collected fecal sample is in the laboratory and maintained under optimal conditions (Duszynski and Wilber 1997), sporulation of most mammalian coccidia occurs best between 20°C–23° C. Exceptions include some tropical species such as *Cyclospora cayetanensis,* which sporulates best at 37° C. Once sporulated, the oocysts of some mammalian species can remain viable and infective in 2% $K_2Cr_2O_7$ 4–5 years (D.W. Duszynski, personal observation). When oocysts are exposed to the natural conditions of their external environment, they remain viable and infective from as little as 49 days up to 86 weeks, dependent upon the species and the interplay of sunlight, shade, and vegetation (Warner 1933; Farr and Wehr 1949; Koutz 1950; Dorney 1962; Wilber et al. 1994a).

The role that naturally occurring soil organisms (e.g., mites, insects, earthworms) may play as mechanical vectors is virtually unknown. Recently, however, Goodwin and Waltman (1996) demonstrated that darkling beetles (*Alphitobius diaperinus*) collected directly from chicken broiler house soils could transmit viable coccidial infections to 6 of 7 SPF (specific pathogen free) chicks inoculated with homogenates from 75 beetles. Another area in desperate need of further study is the mechanisms coccidian species use to overwinter in hibernating mammals (Anderson 1971) and the importance of those mechanisms to the maintenance of coccidian populations in such hosts.

HOST SPECIFICITY. Host specificity is defined (Roberts and Janovy 1996) as the "degree to which a parasite is able to mature in more than one host species." Strict specificity means that one coccidian

species will only infect one host species. In reality, this condition rarely, if ever, exists in nature because it would not be to the advantage of the parasite to so limit its reproductive opportunities, and most coccidia probably are infective to different species, at least within the same host genus. Complicating the issue, the degree of specificity seems to vary from host group to host group. For example, *Eimeria* from goats cannot be transmitted to sheep and vice versa (Lindsay and Todd 1993), but the *Eimeria* from cattle (*Bos*) often are found to infect American bison (*Bison*) (Ryff and Bergstrom 1975; Penzhorn et al. 1994), and *Eimeria* that infect certain rodents (Sciuridae) seem to easily cross host generic boundaries (Todd and Hammond 1968a,b; Wilber et al. 1998). Some coccidia even have been reported to cross familial lines, but this is rare. De Vos (1970) demonstrated that *E. chinchillae,* originally isolated from the chinchilla, could be experimentally transmitted to seven genera of wild rodents (two families), and Hendricks (1977) said that *Isospora arctopitheci,* a parasite of New World primates, could infect six genera of primates (two families), four genera of carnivores (four families) and one genus of marsupial. We also know that *E. separata* from rats will infect certain genetic strains of mice (Mayberry and Marquardt 1973; Mayberry et al. 1982) and that genetically altered (Rose and Millard 1985) or immunosuppressed mammals (Todd et al. 1971; Todd and Lepp 1972; Nowell and Higgs 1989; Aly 1993) are susceptible to infection with *Eimeria* spp. to which they otherwise might be naturally resistant. Thus, numerous biotic interactions between host and parasite must contribute, in concert, to the host specificity (or lack thereof) in the coccidia, especially the genetic constitution of both participants.

Clinical Signs. Most mammals pass oocysts in their feces, sometimes in large numbers under natural conditions, with no apparent ill effects. Mention of obvious signs of illness due to coccidiosis in wild mammals is rare in the literature (e.g., Tanabe 1938; Beveridge 1993). Almost all the information known about the disease state, coccidiosis, comes either from experimental work with domestic or laboratory mammals or from wild, zoo, or domestic stocks where overcrowding, stress, and easy fecal-oral contamination are factors. Both experimentally driven coccidiosis and that resulting from overcrowded conditions result in hosts becoming exposed to massive numbers of sporulated oocysts, which they are unlikely to acquire under natural conditions, but which can graphically demonstrate the clinical symptoms associated with heavy coccidial infections: fever, diarrhea (sometimes with blood), weight loss, abdominal tenderness and cramping, nervous distress, dehydration, anorexia, emaciation, and weakness. Symptoms occur because coccidia first change the integrity of the host enterocyte in which they live and reproduce asexually (Sheppard 1974), thus interfering with digestion and absorption (Stein and Marquardt 1973; Duszynski et al. 1982). In modest to heavy infections they can change the architecture of the intestinal villi themselves and/or the length of the crypts (Fernando and McCraw 1973; Duszynski et al. 1978a); they later destroy the host's intestinal cells, sometimes whole sections of epithelial lining, making the host more susceptible to bacterial invasion (Li et al. 1996) and allowing increased flow of tissue fluid and blood into the intestinal lumen (Bailey 1994).

Pathology and Pathogenesis. Factors that affect the pathogenesis of coccidial infections in wild mammals include at least the following: the number, strain, age (=viability), and species of sporulated oocysts ingested; the age, sex, strain/breed of host; the site of development within the host; the nutritional and immune status of the host; occupation by other parasites and microbes that may compete for space or other host resources with the endogenous stages of the parasite; the behavior and feeding habits of the host; and the coevolutionary process of host and parasites that unite all of these factors and their interactions. Many of these factors have been discussed elsewhere (Fernando 1982; Duszynski 1986; Lindsay and Todd 1993; Li et al. 1996).

The endogenous development of mammalian coccidia usually takes place within specific sites and cells of the gastrointestinal tract of their host. Since merogony is multiplicative, the number of viable oocysts ingested and the location of meronts within the gut are important early determinants of pathology in naive or susceptible hosts. Although most coccidia develop in villus enterocytes, some can develop in crypt enterocytes or cells within the lamina propria (e.g., *E. bovis* in cattle); it is these species that can cause the most damage to the intestinal mucosa. Development in villus enterocytes may result in villus atrophy (Fernando 1982) or elongation (Duszynski et al. 1978a), often accompanied by changes in crypt depth and abnormal epithelial differentiation such as hyperplasia. Such response is common to a wide variety of unrelated intestinal pathogens, leading to the suggestion that altered morphology is an inherent, nonspecific response of the mucosa to damaging agents (Sprinz 1962; Fernando 1982).

As noted, pathology due to coccidia in wild mammals usually is documented in captive wild animals or domesticated (formerly wild) mammals, but seldom in wild mammals under natural circumstances. A few selected examples can serve to illustrate pathogenesis during coccidial infection. In Australia, Barker et al. (1979) documented intestinal pathology when they examined histological sections of small intestine from three wombats (*Vombatus ursinus*) infected with *E. arundeli.* Some of the hosts were wild, some captive; unfortunately, the animal from which the pathology was described was not noted. They found villi over extensive areas of the lower small intestine to be hypertrophied, projecting above uninfected mucosa. The lamina propria also was distended, and many mononuclear inflammatory cells were dispersed among the gametocytes. Although the changes in gross

appearance and histological changes associated with gamogony were striking, "none of the animals had diarrhea or other signs of gastrointestinal disease. The intestinal epithelium was intact and inflammatory infiltrates were moderate and chronic, indicating little pathogenicity in animals examined." However, *E. arundeli* is able to cause disease in captive wombats. Hum et al. (1991) documented disease in two captive juveniles (*V. ursinus*) infected with the parasite. One animal had diarrhea and the second had soft feces, lost weight, and later died. Postmortem tissue sections showed massive gametocytes in hypertrophic cells of the lamina propria, distended villi, and grossly visible, thickened regions of the mucosa over extensive areas of the small intestine. The authors concluded, "heavy infections may be pathogenic under some circumstances." In several species of the larger kangaroos in Australia, coccidiosis frequently takes a peracute form in which the animal is found dead after few premonitory signs. At necropsy, severe hemorrhagic enteritis is found, with blood throughout the small intestine, but contents of the large intestine seem unusually normal (Beveridge 1993).

Not all coccidia are limited to cells of the gastrointestinal tract. The ubiquitous *Eimeria stiedai,* for example, undergoes its endogenous development in epithelial cells of the bile duct and in parenchymal cells of the liver of rabbits. Light infections tend to be unapparent, but heavy infections can result in serious morbidity and mortality, especially in younger animals. Similarly, endogenous stages of *Cyclospora talpae* occur in the liver of the European mole, *Talpa europaea* (Pellérdy and Tanyi 1968). Dubey (1986) found meronts, gamonts, and oocysts in the villous epithelium and submucosal glands of the gall bladder of a commercial dairy goat in Montana that was infected by an unidentified *Eimeria* sp. The infection was localized and did not extend into the liver, no stages were seen in sections of intestine, and no oocysts were found in the feces. Other mammalian coccidia also are known to develop outside the gut, including a coccidium affecting the placenta of the hippopotamus (McCully et al. 1967; Kuttin et al. 1982); a species found in the epididymus of elk (Hrudka et al. 1983); *E. neitzi,* which causes uterine coccidiosis in the impala (McCully et al. 1970); *E. genitalia,* reported by Arcay (1994) to have developmental stages in the epididymis, seminal vesicles, vagina, uterus, and oviducts of hamsters (*Cricetus cricetus*); meronts of *E. riedmuelleri* reported in the bile ducts of chamois (*Rupicapra rupicapra*) by Desser (1978) and later confirmed by Brunnett et al. (1992); and a goat reported by Mahmoud et al. (1994) that died of liver failure attributed to lesions due to coccidiosis. Meronts, gamonts, and oocysts were seen in bile duct epithelium. Granulomas in the liver were composed of oocysts and macrophages encapsulated in a fibrous capsule. Hepatic lymph nodes had oocysts and macrophages diffusely scattered in them. Oocysts of *Eimeria caprina* and *E. alijevi* were identified in the bile, but only oocysts of *E. christenseni* were seen in the feces. In Australian marsupials, hepatic coccidiosis occurs in the Tammar wallaby (*M. eugenii*), and in the western gray kangaroo (*M. fuliginosus*), large meronts associated with focal hemorrhage were found in the pyloric antrum (Beveridge 1993). This opens a related issue that may be pertinent to the discussion on pathogenesis. Unlike the gut, which is a highly plastic, adaptable organ (Dowling and Riecken 1974), other tissues and cells may be more susceptible to pathogenesis by coccidia developing in them.

Diagnosis. In most instances when the host is not to be killed, the diagnosis of a coccidial infection in a wild mammal depends upon demonstration of oocysts in the feces. Initial handling of the sample in the field is critical so that oocysts, if present, can be brought back to the laboratory and allowed to sporulate under favorable conditions (see Duszynski and Wilber 1997). It is necessary for the oocysts to sporulate completely before a specific identification can be made. Once this has been accomplished, sporulated oocysts must be separated from the fecal debris and studied in detail. There are many ways to do this, and there is a rich and lengthy literature, comparing various concentration techniques (sedimentation, flotation) in a variety of fluids, on how to best isolate oocysts from feces (Faust et al. 1939; Farr and Luttermoser 1941; Gill 1954; Ryley et al. 1976; Greve 1989; Moitineo and Ferreira 1992; Arjomandzadeh and Dalimi 1994); methods for cleaning, purifying, and concentrating oocysts (Sharma et al. 1963; Wagenbach et al. 1966; Vetterling 1969; Smith and Ruff 1975; Dulski and Turner 1988); suggestions on how best to count oocysts (Long and Rowell 1958; Dorney 1964); and even methods for staining oocysts (Crouch and Becker 1931; Berland and Højgaard 1981; Markus and Bush 1987; Ashraf and Nepote 1990). Recently, Price (1994) compiled a comprehensive manual of techniques that can be used to isolate the transmission stages, including coccidian oocysts, of intestinal parasites from host fecal material.

In our experience, especially when processing small amounts of feces from large numbers of mammals, sporulated oocysts can be conveniently and efficiently separated from potassium dichromate (2% w/v $K_2Cr_2O_7$ in water) solution by suspending a 1–3-ml aliquot in a modified Sheather's sugar solution (500 g sucrose, 350 ml tap water, 5 ml phenol) and centrifuging 5 minutes at 1500 rpm (= 225 *g*) (see Duszynski and Wilber 1997, for details).

Recently, modern molecular tools [e.g., polymerase chain reaction (PCR), random amplified polymorphic DNA (RAPD)] that are used to study phylogenetic relationships among the coccidia (e.g., Relman et al. 1996; Barta et al. 1997; Pieniazek and Herwaldt 1997) have been employed to detect and identify coccidia, which are important in veterinary and human parasitology (Comes et al. 1996; Yoder et al. 1996). The nested PCR assay, for example, is reported to be able to detect as few as 10–50 oocysts of *Cyclospora cayetanensis* in human stools (Yoder et al. 1996).

The endogenous (asexual and/or sexual) stages in a coccidian life cycle often can be visualized in cells from an intestinal biopsy that has been properly fixed, embedded, sectioned, stained, and mounted on microscope slides. However, there are inherent dangers in the interpretation of such material. First, the endogenous stages of the vast majority of mammalian coccidia (98%) are unknown and thus cannot be directly linked to most species' oocysts; second, stages of merogony found in enterocytes are not necessarily the progenitors of the oocysts seen in the feces—they may represent the stages of another coccidium that has not yet reached gamont formation and oocyst production; and third, we now know that certain endogenous stages of a growing number of coccidian species may not be completely confined to the gastrointestinal tract. For example, Lotze et al. (1964) infected both sheep and goats with sporulated oocysts of *Eimeria arloingi, E. faurei,* and *E. ninaekohlyakimovi* of sheep origin; 13–18 days postinfection they found schizonts (= meronts), presumably of coccidial origin, in the enlarged mesenteric lymph nodes of both sheep and goats. This raises the question whether or not coccidial stages commonly occur in areas of the host's body besides the "regular" sites of their development in gut epithelium (also see Mottalei et al. 1992). Such stages have been well documented for the isosporan spp. of dogs and cats (see review, Lindsay et al. 1997a), for *Isospora belli* in humans (Lindsay et al. 1997b), and for at least one rodent *Eimeria* (Mayberry et al. 1989). In an intriguing note that has never been substantiated or followed up, Cable and Conway (1953) reported gametocytes of a coccidium in the mammary glands of a shrew (*Sorex paulustris*). The confirmed existence of this variety of tissue stages raises additional questions concerning the biology of the coccidia. Are such stages capable of producing, or responsible for, relapse when the host becomes stressed or immunosuppressed? Can the coccidia also be transmitted vertically? These are very fertile areas for future studies on mammalian coccidia.

Immunity. Infection of wild mammals by species of coccidia generally will result in a protective immune response that is specific to that coccidian species. Thus, if a host is infected for the first time with coccidia A, the parasite should go through normal endogenous development in the epithelium of the host, and oocysts will be discharged in the feces. The number of oocysts discharged and the length of time they are shed (the patent period) are dependent upon the number of sporulated oocysts in the initial infective dose, among other things. Later, if the same host becomes exposed again to A and also to coccidia B, there will be some protective immunity against A, but not against B. This protective response can be judged by the reduction or absence of oocyst production for species A and a general lack of clinical signs after challenge. Since wild mammals are probably exposed to thousands of oocysts of many different coccidian species on a daily basis, the immunity that develops as a result of such regular exposure probably is the most important factor in keeping animals in their natural environment free of disease. The literature on immunity to coccidia in general, and on immunity in mammals specifically, is voluminous, with most of the work done either with the bovine coccidium, *E. bovis,* or with several rodent coccidia that can be manipulated easily in the laboratory in either rats (*E. nieschulzi*) or mice (*E. falciformis, E. ferrisi, E. papillata*).

Both the sporozoites that excyst from an oocyst/sporocyst propagule to infect endothelial cells and the merozoites that develop intracellularly via multiple fission and then infect yet other endothelial cells are antigenic and stimulate the host's immune response; in fact, sporozoites and merozoites from the same parasite species seem to share many antigens (for review, see Lindsay and Todd 1993). Both arms of the immune system, humoral (serum antibodies) and cellular immunity, are manifested in the host's response to these foreign invaders (Rose 1974; Rose 1984, 1987; Rose et al. 1984; J.B. Rose et al. 1988; Lindsay and Todd 1993).

Although most coccidial infections induce a strong humoral response, circulating serum antibodies are thought to play only a minor role in impacting coccidial infections. However, locally produced antibodies (IgA-containing cells in the villi under the epithelium and IgM-containing cells deeper in the lamina propria) may present a more meaningful response to the parasite, although the exact mechanism of this effect is not understood. During infections in mice with *E. falciformis,* the locally produced IgA was found to be reactive with other stages in the life cycle (e.g., sporocysts, oocysts), but was parasite-specific in that antibodies failed to cross-react with stages of a second species, *E. ferrisi* (Douglas and Speer 1985). This, despite the fact that Lindsay et al. (1991), Tilahun and Stockdale (1982) Hughes et al. (1989), and others have shown there are surface antigens that are common among some mammalian eimerias.

The evidence is strong that immunity following infection with coccidia (at least *Eimeria* spp.) is cell-mediated (Rose and Hesketh 1979; Rose et al. 1979, 1985; Stockdale et al. 1985); this evidence comes primarily from studies with immune-deficient animals, such as nude (athymic) mice, and with T- and B-cell depleted animals (Lindsay and Todd 1993). Athymic animals have more severe primary infections than wild type animals and have little or no resistence to challenge infections. In mice, immunity can be adoptively transferred using either splenic or, more optimally, mesenteric lymphocytes (M.E. Rose et al. 1988a,b). In addition, depletion of CD4+ cells following administration of anti-Thy-1.2 antibodies abrogates the protective immunity to challenge *E. falciformis* infections (see M.E. Rose et al. 1988b; Stiff and Vasilakos 1990). These results imply that immunity to coccidiosis, at least in rodents, is mediated through CD4+ cells.

Depletion of CD8+ cells in mice infected with *E. vermiformis* had no effect on oocyst production during

primary infections, and there was only a slight increase in oocyst production during secondary infections. However, identical experiments in mice during *E. pragensis* infections resulted in a slight decrease in oocyst production during the primary infection and significant increases in oocyst production during the secondary infection (Rose et al. 1992). Although the exact mechanism by which this phenomenon occurs is unknown, Lillehoj and Trout (1994) suggested that CD8+ cell depletion may increase the severity of challenge infections by eliminating cytotoxic cells that would normally target the infected cells and limit parasite replication.

Neutralization of endogenous IFN-γ (interferon-gamma) by treating mice with anti-IFN-γ has been shown to have a variety of effects that depend, in part, on the species of coccidium studied. Following administration of anti-IFN-γ, enhanced oocyst output was observed during primary *E. vermiformis* infections, whereas no difference was noted during *E. pragensis* infections (M.E. Rose et al. 1989, 1991). Whichever coccidium was studied, however, anti-IFN-γ treatment was not found to prevent development of resistance to challenge, nor did it affect previously established immunity. These data imply that even though IFN-γ may sometimes modulate the intensity of primary infections, other types of immune mechanisms that may affect the intensity of a coccidial infection appear unaffected.

In nature, parasites tend to be overdispersed; that is, a few individuals in a host population bear a majority of the parasites (Roberts and Janovy 1996). Thus, coccidia in wild mammals often are found infecting hosts that also are infected with other parasites; the question arises whether there will be interactions, mediated by the immune response, among the several parasite species. Intrageneric interactions between two eimerias have been documented only once (Duszynski 1972), but intergeneric interactions have been demonstrated between coccidia and nematodes. Duszynski et al. (1978b) were the first to demonstrate that *Eimeria nieschulzi* could suppress the rejection of *Trichinella spiralis* in immunized rats that were concurrently infected. Suppression of the immune response to *Nippostrongylus brasiliensis,* another nematode, also has been demonstrated during concurrent infections with *E. nieschulzi* (Bristol et al. 1983, 1989) and with *E. separata* (Mayberry et al. 1985). Castro and Duszynski (1984) showed that *E. nieschulzi* has the ability to reduce the systemic inflammatory response by interfering with some phase of directed leukocyte migration. Conversely, Stewart et al. (1980) reported that rats inoculated with *T. spiralis* during primary infections with *E. nieschulzi* expelled these nematodes more rapidly than in comparable control animals. Thus, the ability to modulate a host's immune and/or inflammatory response may be a generalized phenomenon, at least in rodents infected concurrently with nematodes and *Eimeria* spp. This is an area of experimental parasitology that deserves attention.

Prevention and Control. A discussion on the prevention and/or control of access to sporulated oocysts does not seem applicable to wild mammals in their natural habitats, under most circumstances. However, over coevolutionary time, hosts may have evolved behavioral adaptations within their specific microenvironments that help them prevent or control contact with infective oocysts. To our knowledge, there is only one reference to lend credibility to this notion. Doran (1953), in a detailed and intriguing survey in California, livetrapped, over 3 years, 611 kangaroo rats (*Dipodomys* spp.) representing 6 species and 11 subspecies: *D. agilis agilis* (12 rats); *D. deserti deserti* (10); *D. heermanni morroensis* (19); *D. h. swarthi* (10); *D. h. tularensis* (15); *D. merriami merriami* (197); *D. nitratoides brevinasus* (21); *D. panamintinus caudatus* (20); *D. p. leucogenys* (33); *D. p. mohavensis* (251); and *D. p. panamintinus* (23). Only 22/251 (9%) *D. p. mohavensis* were found to be infected, all with a single species, *Eimeria mohavensis.* However, when 150–270 sporulated oocysts of *E. mohavensis* were administered to between 9 and 42 uninfected rats of each of the 11 subspecies under laboratory conditions, all 11 subspecies became infected. In addition, interestingly, the 20 *D. m. merriami* that were cross-infected produced almost twice as many oocysts during patency as did the 42 *D. p. mohavensis* when inoculated with equivalent numbers of oocysts. In other words, in this very large survey, only 1 of 11 subspecies was infected naturally with *E. mohavensis,* but all 11 subspecies were susceptible under laboratory conditions, and 1 subspecies, never found to be infected naturally (0/197 *D. m. merriami*), was more susceptible to the parasite than its presumed normal host. Is it possible that the other 10 subspecies have evolved a behavioral mechanism to avoid contact with sporulated oocysts in their natural environment and thus prevent/control infection? This is another area that deserves further study.

Treatment. Most or all of the drugs marketed for use against coccidia infections in mammals were first used to treat avian coccidiosis (McDougald 1982). Anticoccidials function by biochemically altering an important chemical pathway in the metabolism of the parasite without affecting a similar chemical pathway in the host to the same degree. The drugs most often used to treat coccidiosis in mammals (domestic, zoo, and captive animals) include the ionophores (interfere with membrane function by altering ionic gradients) such as monensin, lasalocid, and salinomycin; the sulfonamides (interfere with folic acid synthesis) such as trimethoprim; amprolium (thiamine-antagonist that interferes with cofactor synthesis); clopidol (a pyridone compound that interferes with energy metabolism in sporozoites or merozoites); robenidine [a bis-(benzylidineamino) guanidine that interferes with energy metabolism by inhibiting oxidative phosphorylation in the mitochondria (Wong et al. 1972)]; and decoquinate (blocks mitochondrial electron transport) (McDougald 1982; Gutteridge 1993). Drug resistance

to anticoccidials is a major problem in controlling potential disease-producing species (e.g., *E. arlongi, E. bovis, E. stiedai*). Since drug resistant forms sometimes can be selected out in the absence of the drug to which they are resistant, diet-formulating companies often rotate the coccidiostats they incorporate into their diets to minimize this problem (Gutteridge 1993). Providing medicated feed or water is the most reliable means of control when mammals are contained in some way, but seems impractical for most wild mammals.

Public Health Concerns. Unlike *Cryptosporidium,* which can be a serious zoonosis (see below), there is no evidence that *Eimeria* or *Isospora* spp. of wild mammal origin can infect humans; not even *I. arctopitheci,* which seems to have the broadest host range for any known species in these three genera (Hendricks 1977). However, since 1985 there has been a growing literature on "cyanobacterium-like bodies" (CLBs) identified worldwide in the feces of immunocompetent and immunocompromised humans with diarrhea. In 1993, these CLBs were finally identified as coccidian oocysts in the genus *Cyclospora* (Ortega et al. 1993). Recently, Smith et al. (1996) found *Cyclospora* oocysts in the feces of all 37 baboons (*Papio*) and in 1 of 15 chimpanzees (*Pan*) in Gombe National Park, Tanzania. They stated that Dr. R.W. Ashford, Liverpool School of Tropical Medicine, confirmed that the oocysts they found "were identical to those described previously in human beings" as *C. cayetanensis.* If true, this suggests that in East Africa, higher primates may be an animal reservoir for human infection. However, the opposite also may be true since Smith et al. (1996) said that previous studies in Gombe suggested that the number of parasite species isolated from baboons and chimps in the park was greatest in those groups that had the most frequent human contact.

Domestic Animal Health Concerns. The importance of mammalian wildlife in their natural habitat has only recently begun to be appreciated. However, as human population continues to increase and agricultural development accelerates, attempting to keep pace, the potential for domestic animals to become infected by coccidian parasites maintained in wild reservoir hosts always remains a possibility (Roth 1972). For example, elk, deer, or bison can serve as reservoirs of coccidia or other parasites (helminths, mites, ticks, fleas, lice) for domestic livestock (Worley et al. 1969; Penzhorn et al. 1994); wild canids and felids can serve as reservoirs for domestic dog and cat parasites (Davidson et al. 1992a,b), including *Isospora* spp.; opossums may serve as hosts for parasites and diseases known to occur in ruminants in specialized, confined environments such as Kangaroo Island near Adelaide, South Australia (O'Callaghan and Moore 1986); and cottontail (*Sylvilagus* spp.) and jack (*Lepus* spp.) rabbits can serve as reservoirs for domesticated rabbit (*Oryctolagus* sp.) coccidia.

Management Implications. All natural populations of wild mammals surveyed for coccidia are found to be infected with at least one, but usually several, species unique to that host group, but the vast majority are not pathogenic under such conditions. The application of management practices to prevent outbreaks of coccidiosis in wild mammals should be focused on zoo and/or captive mammal situations. New animals should be quarantined several weeks before being introduced into a closed, captive environment with conspecifics or congenerics, and their feces should be monitored for the presence of (generally unsporulated) oocysts on a daily basis or at least several times each week. They should not be placed with other captive hosts until oocysts are no longer found in their feces. Oocysts also can be transferred to, and introduced into, captive mammal populations mechanically by flying vertebrates or invertebrates. Mammals in such situations should never be kept under crowded conditions to avoid potential outbreaks of disease.

FAMILY CRYPTOSPORIDIIDAE

Life History. Currently, seven named *Cryptosporidium* spp. are recognized as valid, four of which occur in mammals (Fayer et al. 1997) (Table 16.12). However, additional isolates are certain to be assigned names in the future, including at least two from mammals. *Cryptosporidium parvum* (Tyzzer 1912) primarily targets the ileum of humans and neonate animals and is responsible for > 99% all reported cases of diarrheal illness due to cryptosporidiosis in mammals. At least 79 mammalian species were reported recently as suitable hosts for the parasite (O'Donoghue 1995), and this list grows monthly.

More is known about the development and life cycle (Fig. 16.11) of *C. parvum* than about any other member of the genus. Infection begins with ingestion of the environmentally resistant oocysts, which are small, measure 5.2 x 4.6 μm (4.8–5.6 x 4.2–4.8 μm), and have a shape index of 1.2 (1.0–1.3) (Tilley et al. 1991). Each oocyst contains four sporozoites, which exit from a suture located along one side of the oocyst. The preferred site of infection is the ileum, although other sites also can be colonized. Sporozoites penetrate individual epithelial cells and become enclosed by a thin layer of host cell cytoplasm and membranes. A desmosome-like attachment organelle and accessory foldings of the parasite membranes develop at the interface between the parasite proper and the host cell cytoplasm (Fig. 16.11). This attachment organelle is sometimes referred to as the "feeder organelle." Merogony occurs, resulting in the formation of eight merozoites within the meront. These meronts are termed Type I meronts, and they rupture open to release free merozoites. These merozoites penetrate new cells and undergo another merogony. Type I merozoites are thought to be capable of recycling indefinitely; thus, the potential exists for new Type I meronts to arise continuously.

TABLE 16.12—Known species of *Cryptosporidium* (and synonyms) from mammals[a]

Valid Named and Unnamed Species [Synonyms]	Principal Hosts	Site of Infection	Select Key References
felis sensu lato Iseki, 1979	*Felis catus* (domestic cat)	Small intestine	Asahi et al. 1991, Iseki 1979
muris Tyzzer, 1907	*Mus musculus* (house mouse) *Rattus* spp. (old world rats)	Stomach	Iseki 1986 Iseki et al. 1989; Moriya 1989; Rhee et al. 1991b; Tyzzer 1907, 1910
parvum Tyzzer, 1912	> 90 known mammalian spp.	Small intestine	Current and Reese 1986, Fayer et al. 1997, Tyzzer 1912
[*agni* Barker & Carbonnel, 1974] [*bovis* Barker & Carbonnel, 1974] [*cuniculus* Inman & Takeuchi, 1979] [*enteritides* Qadripur & Klose, 1985] [*enteritidis* Müller, 1986] [*garnhami* Bird, 1981] [*rhesi* Levine, 1980] [*vobis* Iseki, 1979 *lapsus*]			
sp. of Upton and Current, 1985 [*muris* of Upton & Current, 1985]	*Bos taurus* (cattle)	Abomasum	Anderson 1987, 1988, 1990, 1991a; Esteban and Anderson 1995
wrairi Vetterling, Jervis, Merrill & Sprinz, 1971	*Cavia porcellus* (guinea pig)	Small intestine	Angus et al. 1985; Chrisp et al. 1990, 1992; Tilley et al. 1991; Vetterling et al. 1971a,b

[a]*C.* sp Bearup, 1954 from *Canis familiaris* (a dingo), *C.* sp. Dubey and Pande, 1963 from *Felis chaus* (jungle cat), and *C. vulpis* Wetzel, 1938 from *Vulpes vulpes* (fox) are misidentifications of *Sarcocystis* spp.; *C. curyi* Oggassawara, Benassi, Larsson and Hagiwara, 1986 from *Felis catis* (cat) is most likely a misidentification of nematode eggs.

Some Type I merozoites are triggered into forming a second type of meront, the Type II meront, which contains only four merozoites. Once liberated, the Type II merozoites appear to form the sexual stages. Some Type II merozoites enter cells, enlarge into the macrogametocyte, and then form macrogametes. Others enter cells to become the microgametocyte that undergoes multiple fission to form 16 nonflagellated microgametes. Microgametes rupture from the microgametocyte and penetrate macrogametes, forming a zygote. Sporogony occurs, resulting in the production of four sporozoites; thus, sporulated oocysts are passed in the feces into the environment.

About 20% of the oocysts produced in the gut fail to form an oocyst wall, and only a series of membranes surround the developing sporozoites. These "oocysts," devoid of a true wall, are sometimes termed "thin-walled oocysts." It is believed that the sporozoites produced from these thin-walled oocysts can excyst while still within the gut and infect new cells. Thus, *C. parvum* appears to have two autoinfective cycles: (1) continuous recycling of Type I merozoites and (2) sporozoites rupturing from thin-walled oocysts.

Development of *C. parvum* occurs more rapidly than many textbooks imply, and each generation can develop and mature in as little as 14–16 hours. Due to the rapidity of the life cycle and to the autoinfective cycles, huge numbers of organisms can colonize the intestinal tract in several days. The ileum soon becomes crowded, and secondary sites, such as the duodenum and large intestine, are often infected. In immunosuppressed individuals, parasites sometimes can be found in the stomach, biliary and pancreatic ducts, and respiratory tract. The prepatent period of *C. parvum* is generally 4 days, and patency generally lasts 7–10 days in immunocompetent hosts, but may become prolonged in immunosuppressed animals.

A morphologically similar species, *C. wrairi* Vetterling, Jervis, Merrill, and Sprinz 1971 *sensu lato,* also infects the small intestine, but has a high degree of specificity for the guinea pig, *Cavia porcellus.* Oocysts of this species are virtually identical to those of *C. parvum,* and measure 5.4 x 4.6 µm (4.8–5.6 x 4.0–5.0 µm) with a shape index of 1.2 (1.0–1.3) (Tilley et al. 1991). Although the parasite readily infects guinea pigs, it is weakly transmissible to ruminants and suckling mice (Angus et al. 1985; Tilley et al. 1991; Chrisp et al. 1992, 1995); it never has been reported from natural populations of guinea pigs in the wild, however. The life cycle was studied in detail by Vetterling et al. (1971a,b), and it appears nearly identical to that of *C. parvum.*

A third intestinal species, *C. felis* (Iseki 1979) *sensu lato,* also infects the small intestine and has oocysts similar in size to, and perhaps slightly smaller than, *C. parvum.* Iseki (1979) studied the life cycle in detail and reported oocysts to measure about 5 x 4.5 µm. Asahi et al. (1991) reported oocysts as 4.5 µm in diameter and Arai et al. (1990) as 4.7 x 4.3 µm. The life cycle appears virtually identical to that of *C. parvum* (Iseki 1979). Both Iseki (1979) and Asahi et al. (1991) were successful in transmitting feline-derived oocysts back

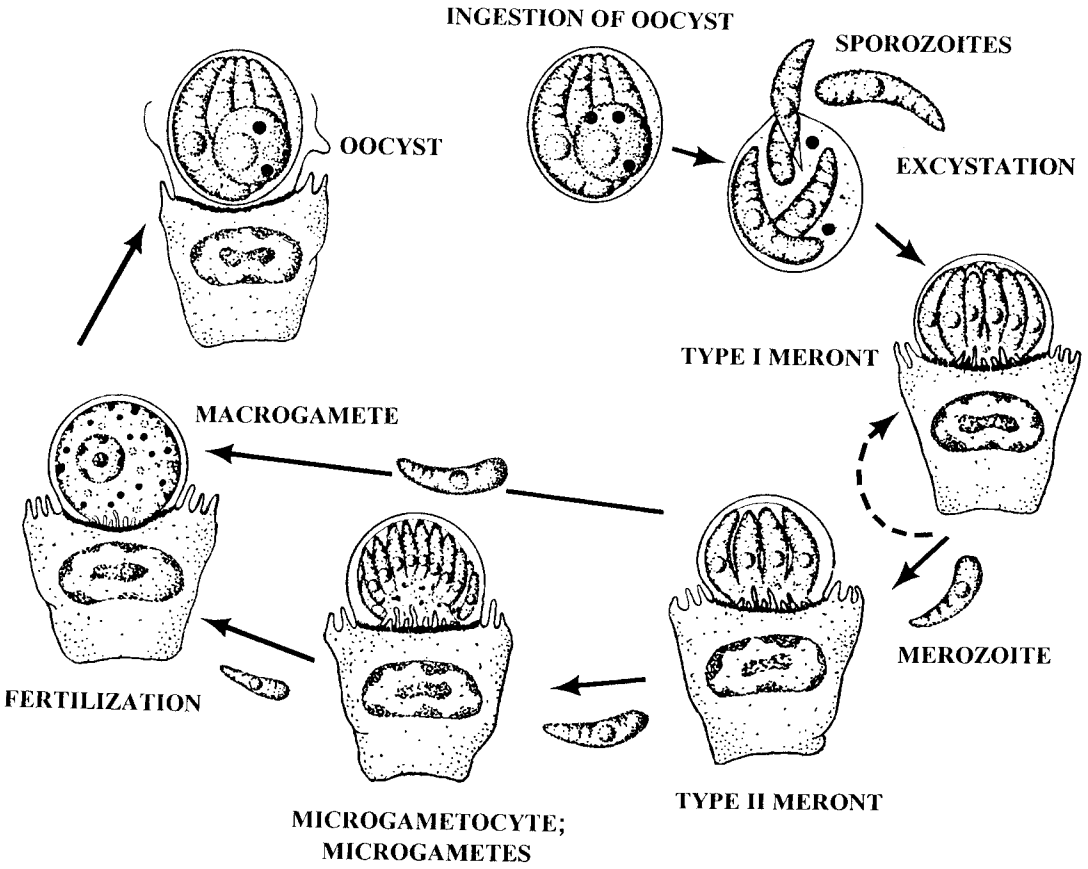

FIG. 16.11—Line drawing showing the life-cycle stages of *Cryptosporidium parvum.*

to cats, but failed to infect other animals including adult, suckling, or immunosuppressed mice, rats, guinea pigs, or dogs. These data suggest that this parasite may be specific only for felids and, if so, probably deserves true specific status. Prepatency appears to be 5–6 days, and some cats develop chronic infections and shed oocysts over long periods (Iseki 1979; Asahi et al. 1991). Mtambo et al. (1996) stated that they were able to infect two lambs, but not suckling mice, with oocysts derived from cats, but control lambs were lacking in the study. The wide range in prepatency in the two lambs (3 and 10 days) is unusual, and infections may simply have been spurious.

Cryptosporidium muris (Tyzzer 1907), the type species, develops in the gastric glands of Old World mice and rats (Tyzzer 1907, 1910; Iseki 1986; Moriya 1989; Aydin 1991; Rhee et al. 1991a,b; Chalmers et al. 1994; özkul and Aydin 1994). It also has been reported from *Phodopus roborovskii,* the desert hamster (Pavlásek and Lávika 1995). Oocysts are infective for both juvenile and adult animals and are larger than *C. parvum, C. wrairi,* or *C. felis,* measuring 8.4 x 6.3 μm (7.5–9.8 x 5.5–7.0 μm) with a shape index of about 1.3 (Iseki 1986). Although it is likely that more than one type of asexual stage occurs, Tyzzer (1907, 1910) only reported a single autoinfective merogonous generation from the gastric mucosa, and no one yet has reported additional types. Both juvenile and adult rodents can be infected, and prepatency approaches 6 days (Rhee et al. 1991b). Peak oocyst production occurs between 15 and 31 days, with patency exceeding 2 months (Rhee et al. 1995). Experimental transmission studies have shown that some animals in addition to rodents also can become infected; these include dogs, guinea pigs, rabbits, and especially cats (Iseki et al. 1989; Aydin 1991). *Cryptosporidium* spp. from camels and rock hyrax also may represent *C. muris* as they both are similar in size to the type species and are transmissible to rodents (Anderson 1991b; Fayer et al. 1991; Esteban and Anderson 1995).

A large, abomasal form commonly found in juvenile and adult cattle and water buffalo sometimes is called *C. muris* or *C. muris*–like (Upton and Current 1985; Anderson 1987, 1988, 1990, 1991a; Esteban and

Anderson 1995; Nagy 1995; Pavlásek 1995; Araújo et al. 1996; Bukhari and Smith 1996). However, oocysts are slightly smaller and less elongate than *C. muris* and measure 7.4 x 5.6 μm (6.6–7.9 x 5.3–6.5 μm), with a shape index of 1.3 (1.1–1.5) (Upton and Current 1985). Experimental transmission studies in cattle result only in a limited number of successful infections (Anderson 1988). Pavlásek (1994) suggested that the parasite may be transmissible to mice, but other investigators have not been able to reproduce these data (Esteban and Anderson 1995). One study suggested that horses also may pass this parasite (da Silva et al. 1996). The life cycle of this parasite is unknown.

Epizootiology. *Cryptosporidium parvum* has been reported to occur worldwide on all continents except Antarctica. Fayer et al. (1997) list 95 countries where human cryptosporidiosis has been reported to be common in both humans and domestic animals, especially ruminants. Little epizootiology data are available for the parasite in wildlife, and most information is confined to sporadic case reports or outbreaks in captive herds, but evidence suggests that the organism is widespread throughout wildlife populations.

Epidemiologic studies suggest that major outbreaks of cryptosporidiosis occur during increased rainfall and/or high humidity (D'Antonio et al. 1985; Mathan et al. 1985; Shahid et al. 1985, 1987; Mata 1986; Cruickshank et al. 1988; Brown et al. 1989; Hayes et al. 1989; Pal et al. 1989; Steele et al. 1989; Mølbak et al. 1990, 1993; Skeels et al. 1990; Mangini et al. 1992; Leland et al. 1993; MacKenzie et al. 1994; Gennari-Cardoso et al. 1996). This often correlates with birthing of animals in the spring, although differences in local climate and rainfall, or point source contamination, can affect results. Dagan et al. (1991) noted *Cryptosporidium* to be more prevalent during the hot and dry season in southern Israel, but Clavel et al. (1996) found no seasonal variation. Generally, however, numbers of viable oocysts in wildlife populations in the Western Hemisphere should be highest in the spring because of the increased numbers of neonates and increased rainfall.

Spontaneous or experimental infections can result in diarrhea in neonate and immunosuppressed primates. Known hosts include baboon (Miller et al. 1990), *Cercopithecus* spp. (Gomez et al. 1992), lemur (Gomez et al. 1992), marmosets (Kalishman et al. 1996), *Macaca* spp. (Kovatch and White 1972; Cockrell et al. 1974; Wilson et al. 1984; Russell et al. 1987; Miller et al. 1990), mangabey (Gomez et al. 1992), orangutan (Wang and Liew 1990), patas monkeys (Gomez et al. 1992), spider monkeys (Gomez et al. 1992), squirrel monkeys (Bryant et al. 1983), and tamarins (Heuschele et al. 1986). Cryptosporidiosis has not been reported in immunocompetent, adult primates, nor have infections from wild populations been reported.

Cervids appear to be highly susceptible to *C. parvum,* and significant morbidity and mortality can occur. Infections have been reported in axis (*Axis axis*), Barasingha (*Cervus duvauceli*), Eld's deer (*Cervus eldi*), fallow deer (*Dama dama*), mule deer (*Odocoileus hermionus*), red deer (*Cervus elephus*), roe (*Capreolus capreolus*), sika (*Cervus nippon*), and white-tailed deer (*Odocoileus virginianus*). Most reports of severe diarrhea involve neonates and domestically reared or captive animals (Tzipori et al. 1981a; Angus et al. 1982; Korsholm and Henriksen 1984; Mason 1985; Orr et al. 1985; van Winkle 1985; Heuschele et al. 1986; Angus 1988, 1989; Blewett 1989; Simpson 1992; Fayer et al. 1996a). One study reported a captive white-tailed doe and her fawn passed oocysts, but neither had clinical illness (Fayer et al. 1996a).

In addition to deer, numerous other wild, captive artiodactyls, predominately neonates, have been reported to harbor *C. parvum.* Most reports involve incidental findings, and hosts include addax (*Addax nasomaculatus*), antelope (*Connochaetes taurinus, Hippotragus niger, Kobus ellipsiprymmus*), Barbary sheep (*Ammotragus lervia*), blackbuck (*Antilope cervicapra*), eland (*Taurotragus oryx*), gazelle (*Gazella dama, G. dorcas, G. leptoceros, G. subgutterosa, G. thomsoni*), giraffe (*Giraffa camelopardalis*), impala (*Aepyceros melampus*), llama (*Llama glama*), mouflon (*Ovis orientalis*), nilgai (*Boselaphus tragocamelus*), oryx (*Oryx gazella*), springbok (*Antidorcas marsupialis*), Turkomen markhor (*Capra falconeri*), and buffalo (*Bubalus bubalis, Syncerus caffer*) (Canestri-Trotti and Quesada 1983; Ducatelle et al. 1983; Fenwick 1983; Canestri-Trotti et al. 1984; van Winkle 1985; Heuschele et al. 1986; Crawshaw and Mehren 1987; Iskander et al. 1987; Canestri-Trotti 1989; Hovda et al. 1990; Rodriguez-Diego et al. 1991; Dubey et al. 1992; Gomez et al. 1996). Significant morbidity and some mortality in water buffalo calves have been reported. In Italy, 7% of 229 neonates with diarrhea passed oocysts (Canestri-Trotti and Quesada 1983), and 20%–21% of the neonates in Cuba and Egypt were reported to be infected (Iskander et al. 1987; Rodriguez-Diego et al. 1991).

Equids and other Perissodactyla, including the rhinoceros, also acquire *C. parvum.* Again, diarrheal illness generally is associated only with neonates or immunodeficient animals (Snyder et al. 1978; Tzipori and Campbell 1981; Gibson et al. 1983; Soule et al. 1983; Canestri-Trotti and Visconti 1985; Gajadhar et al. 1985; Lengronne et al. 1985; Carneiro et al. 1987; Chermette et al. 1987, 1989; DiPietro et al. 1988; Fernández et al. 1988; Coleman et al. 1989; Poonacha and Tuttle 1989; Mair et al. 1990; Wang and Liew 1990; Bjorneby et al. 1991b; Eydal 1994; Xiao and Herd 1994a,b; Gomez et al. 1996; Netherwood et al. 1996; da Silva et al. 1996). The parasite was first reported in equids by Snyder et al. (1978), who noted five of six immunodeficient Arabian foals that died of adenoviral infection also harbored *C. parvum.* However, a high percentage of immunocompetent foals also acquire the parasite. Infection rates vary from 2%–60% (Xiao and Herd 1994a,b), and foals seem to be most susceptible between 5 and 20 weeks of age (Xiao and Herd 1994b). Although most studies suggest the prevalence of infec-

tion in older horses is low (Coleman et al. 1989; Xiao and Herd 1994a,b), adult animals can pass oocysts, and a study in France suggested that mares may serve as a source of infection for foals (Chermette et al. 1989). A similar study in North America came to the opposite conclusion (Xiao and Herd 1994b).

Incidental findings of *C. parvum* in other wild, captive, or zoo mammals include reports documenting the parasite in ferrets (Rehg et al. 1988; Gómez-Villamandos et al. 1995); grey fox (Davidson et al. 1992a,b), insectivores (Sinski 1993; Sinski et al. 1993), leopard (Wang and Liew 1990), Malayan bear (Wang and Liew 1990), marsupials (Barker et al. 1978; O'Donoghue 1995; Fayer et al. 1997), monotremes (O'Donoghue 1995), rabbits (Ryan et al. 1986), raccoon (Carlson and Neilsen 1982; Snyder 1988; Martin and Zeidner 1992), and various rodents (Elton et al. 1931; Sundberg et al. 1982; Davis and Jenkins 1986; Yamini and Raju 1986; Isaac-Renton et al. 1987; Yamaura et al. 1990; Pavlásek and Kozakiewicz 1991; Elangbam et al. 1993; Sinski 1993; Sinski et al. 1993; Laakkonen et al. 1994; O'Donoghue 1995; Pavlásek and Lávicka 1995). Nearly all data on *Cryptosporidium* spp. in wild populations is confined to rodent studies. Oocysts were found in 1 of 131 (0.8%) *Microtus agrestis* and 1 of 41 (2%) *Cleithrionomys glareolus* in Finland (Laakkonen et al. 1994). Chalmers et al. (1994) found 19 of 58 (33%) wild mice trapped near Moreton Morrell, United Kingdom, to be passing oocysts, and Elangbam et al. (1993) found developmental stages in the intestinal tract of 1 of 9 (11%) *Sigmodon hispidus* from Pryor, Oklahoma. In Poland, in the district of Mazury Lake, 55 of 275 (20%) *C. glareolus,* 6 of 39 (15%) *Apodemus flavicoliis,* and 5 of 16 (31%) *Sorex araneus* were positive (Sinski et al. 1993). Of 115 *Mus musculus* live-trapped near a calving site in Auburn, Alabama, and placed in captivity 2–3 weeks, 35 (30%) were passing oocysts (Klesius et al. 1986).

Although the majority of reports of *Cryptosporidium* spp. in wildlife appear to be due to *C. parvum,* some information is available about other *Cryptosporidium* spp. Of the two named intestinal species, *C. felis* and *C. wrairi,* only the former is known to occur in natural populations, with the latter reported only from laboratory-reared guinea pigs. Iseki (1979) found 5 of 13 (38%) cats infected in Osaka. Five of 608 (4%) felids were passing oocysts in Tokyo (Arai et al. 1990), and 35 of 871 (4%) cats were shedding oocysts in Austria (Supperer and Hinaidy 1986). In Glasgow, 19 of 235 (8%) and 7 of 57 (12%) cats were found to be passing oocysts (Mtambo et al. 1991; Nash et al. 1993). Because oocysts of *C. parvum* and *C. felis* are indistinguishable and because both have been shown to infect cats, some of the prevalence data actually may represent infections with *C. parvum.*

Several studies suggest that the *Cryptosporidium* sp. from the abomasum of juvenile and adult cattle is widespread. Bukhari and Smith (1996) found 23% of 109 dairy cattle in Scotland to be infected. In the Czech Republic, 4 of 96 (4%) cows were passing oocysts (Pavlásek 1994), and 1.4% of 95,874 randomly collected bovine fecal samples from 12 states in the United States were infected (Anderson 1991a). Overall, samples collected from dairy herds were found to have twice the prevalence of feedlot samples (Anderson 1991a). A total of 4.5% of 887 Holstein-Friesian breed heifers entering the Czech Republic from France and 7.9% of those imported from Germany were passing oocysts (Pavlásek 1995). Although this coccidium may be specific for bovids, Pospischil et al. (1987) reported that captive Mountain gazelles (*Gazella cuvieri*) from the Munich Zoo were infected by an abomasal *Cryptosporidium* sp. similar in size to that reported in cattle.

Cryptosporidium muris has not been reported from natural populations of rodents in the Western Hemisphere, but it is known to occur naturally in Europe and Asia. This includes 3 of 64 (5%) *Rattus* spp. in Osaka (Iseki 1979) and 15 of 58 (26%) mice on a farm in Moreton Morrell, United Kingdom (Chalmers et al. 1994). A *C. muris*–like organism was reported from a Bactrian camel (*Camelus bactrianus*) from the National Zoological Park in Virginia (Anderson 1991b; Fayer et al. 1991). Experimental transmission studies demonstrated that mice, but not calves, could acquire the infection, suggesting that the parasite may truly be *C. muris.* Similar-sized oocysts passed by a rock hyrax at the National Zoological Park also were infective for mice (Esteban and Anderson 1995), and da Silva et al. (1996) reported what may be this parasite from equids in Brazil.

Clinical Signs. Significant illness due to *C. parvum* rarely has been reported from wild-caught animals, but it is common once the animals become captive, when crowding and additional stress become factors. Acute cryptosporidiosis manifests itself in moderate to severe diarrhea, weight loss, abdominal cramping, lethargy, inappetence, and occasionally fever. Severe dehydration may occur, occasionally resulting in electrolyte imbalance and death. In bovids, the disease is typically characterized by high morbidity, but low mortality, and cases involving significant mortality generally involve a second pathogen such as rotavirus or ETEC-K99+ (Fayer et al. 1985; 1997). Cases involving high mortality in the absence of secondary pathogens usually can be traced to an immunodeficient host population or to misdiagnoses (Heine et al. 1984b; Fayer et al. 1997). However, other animals may be more susceptible to the parasite, and significant mortality may occur, especially if additional stress on the animals is incurred.

Immunocompetent animals reported to have significant illness include chinchilla (Yamini and Raju 1986), fawns (Tzipori et al. 1981a; Korsholm and Henriksen 1984; Orr et al. 1985; Heuschele et al. 1986), foals (Gajadhar et al. 1985; DiPetro et al. 1988; Fernández et al. 1988; Coleman et al. 1989; Browning et al. 1991; Xiao and Herd 1994a,b; Netherwood et al. 1996), hamsters (Davis and Jenkins 1986; Orr 1988), primates (Kovatch and White 1972; Cockrell et al. 1974; Wilson

et al. 1984; Russell et al. 1987; Miller et al. 1990), water buffalo (Canestri-Trotti and Quesada 1983; Iskander et al. 1987), and other ruminants (Fenwick 1983; Heuschele et al. 1986; Hovda et al. 1990).

Infections with *C. wrairi* in guinea pigs may range from subclinical to acute, similar to that reported for *C. parvum* in other animals. Clinical signs include diarrhea, dehydration, and weight loss (Angus et al. 1985; Gibson and Wagner 1986). Morbidity and mortality associated with cryptosporidiosis in guinea pig colonies of various suppliers was reported to range from 0%–50% (Gibson and Wagner 1986).

Since both *C. parvum* and *C. felis* are capable of infecting neonate and immunosuppressed cats, and because multiple types of immunosuppressive viruses exist in felids, reports of diarrheal illness due to cryptosporidiosis in cats must be viewed cautiously. It is known, however, that juvenile and adult cats are highly susceptible to *C. felis.* Infections in adult animals generally are chronic and subclinical, even when large numbers of oocysts are shed in the feces (Arai et al. 1990; Asahi et al. 1991).

In mammals, infections with the large species of *Cryptosporidium* infecting the gastric mucosa often are chronic and subclinical. Neither Iseki (1986) or Iseki et al. (1989) noted clinical signs in animals infected with *C. muris,* and Anderson (1987, 1988) reported cattle infected with the abomasal *Cryptosporidium* sp. also were subclinical. However, some animals infected with the latter species had depressed weight gain (Anderson 1987; Esteban and Anderson 1995). One study suggested that dairy cows shedding oocysts may produce less milk than uninfected cohorts, although these differences were not found to be statistically significant (Esteban and Anderson 1995).

Pathology and Pathogenesis. The primary site of infection by *C. parvum* is the distal region of the small intestine, although the cecum, colon, and duodenum also support development. Sometimes parasites can be found in the pancreatic and biliary ducts, as well as the urogenital and respiratory tracts (Sanford and Josephson 1982; Heine et al. 1984a; Pavlásek 1984; Pavlásek and Nikitin 1987; Kaup et al. 1994; Mascarø et al. 1994). However, only in rare instances are these latter sites colonized to any degree in immunocompetent animals. Infections have been associated with villus atrophy and villus fusion, infiltration of the lamina propria by inflammatory cells, and sloughing and degeneration of individual enterocytes (Panciera et al. 1971; Pearson and Logan 1978; Howerth 1981; Tzipori et al. 1981b,c; Angus et al. 1982; Sanford and Josephson 1982; Heine et al. 1984b; Vítovec and Koudela 1988, 1992). Metaplasia of the surface epithelium to cuboidal or low columnar cells has been observed (Howerth 1981; Heine et al. 1984b), and crypts may become dilated and fill with necrotic debris (Powell et al. 1976; Sanford and Josephson 1982). These changes result in reduced absorption of vitamins and sugars (Argenzio et al. 1990; Holland et al. 1992; Nappert et al. 1993; Clark and Sears 1996), and it is likely that enterocyte damage results in impaired glucose-stimulated Na+ and H_2O absorption (Clark and Sears 1996). Since disaccharidase activity is thought to decrease due to the loss of mature enterocytes, it has been postulated that the undegraded sugars also may allow for bacterial overgrowth and a change in osmotic pressure due to the formation of volatile free fatty acids (Holland et al. 1989). Alternatively, the accumulation of nonabsorbed nutrients may lead to a hypertonic condition that also contributes to diarrhea (Holland et al. 1989). Argenzio et al. (1993) suggested that at least some of the diarrhea in piglets experimentally infected with *C. parvum* can be attributed to local prostanoid production. Although the presence of an enterotoxin has been postulated (Garza et al. 1986; Guarino et al. 1994), no definitive evidence exists to conclusively demonstrate that the parasite produces an enterotoxin.

Experimental infections of immunocompetent cats with *C. felis* results in a notable lack of gross pathology and histopathology associated with the digestive tract (Iseki 1979; Asahi et al. 1991). However, infections of guinea pigs with *C. wrairi* induce a pathology similar to that of *C. parvum,* and results range from subclinical to fatal. Angus et al. (1985) noted that infections occur throughout the small intestine and cecum, but are heaviest in the ileum where severe villus stunting and fusion occur. The lamina propria becomes infiltrated with macrophages and eosinophils, and the mucosa becomes covered by a thick, flat layer of cuboidal cells. Similar results have been reported by other researchers (Jervis et al. 1966; Kunstý and Naumann 1981; Gibson and Wagner 1986; Chrisp et al. 1990). Gibson and Wagner (1986) described such macroscopic findings as emaciation, intestinal hyperemia, and serosal edema of the cecal wall.

Although *Cryptosporidium* spp. developing in the stomach generally produce few clinical signs, infections are persistent, and pathology has been observed. Abomasal cryptosporidiosis in cattle results in an abomasum that is enlarged and thickened by ~10%, an increase in the depth of the gastric glands and widening of the gland lumen, and dilation and atropy of some glandular cells (Anderson 1987, 1988). Plasma pepsinogen concentrations also have been reported to be above normal (Anderson 1988). Pathological findings associated with *C. muris* in rodents include enlargement of the lumens of the gastric glands, flattening and atrophy of epithelial cells, and reduction in the number of microvilli (Aydin 1991; Yoshikawa and Iseki 1992; Özkul and Aydin 1994).

Diagnosis. Early diagnostic procedures for *Cryptosporidium* spp. often involved histological processing of biopsy materials, but identification of oocysts passed in the feces is now the primary method of diagnosis. These assays fall under three general categories: microscopic, which includes flotations, smears, stains, and immunofluorescent antibody (IFA) probes; enzyme immunoassays (EIA), usually based on bind-

ing of an antibody to the outer oocyst wall followed by colorimetric detection; and molecular, which include polymerase chain reaction (PCR) and derivitives.

Proper collection and storage of feces is critical for any diagnostic method involving antibodies. Many fixatives and storage solutions change outer-wall antigenicity and must be avoided. Aqueous solutions of potassium dichromate and sodium acetate are known to affect binding of some antibodies (Nichols et al. 1991; Upton 1997), and sedimentation techniques using diethyl ether or chloroform should be strictly avoided whenever IFA or EIA are used. Most commercially available antibody-based tests are designed for parasites that have been either frozen or preserved in 10% formalin.

Chermette and Boufassa-Ouzrout (1988) list 18 published staining techniques for oocysts of *Cryptosporidium* in fecal smears. Arrowood (1997) lists 28 different microscopic techniques, which predominately consist of staining and indirect or direct IFA assays. The techniques that have gained the most popularity for field use are modifications of the original acid-fast techniques, which stain the contents of oocysts with a compromised outer wall bright red, often against a bluish-green background. These techniques are relatively quick and inexpensive and allow for differentiation of *Cryptosporidium* oocysts from yeast spores (Henriksen and Pohlenz 1981; Garcia et al. 1983; Ma and Soave 1983; Bronsdon 1984; Casemore et al. 1984; Pohjola et al. 1985; Ma 1986; Chermette and Boufassa-Ouzrout 1988; Ridley and Olsen 1991; Entrala et al. 1995; Arrowood 1997). Numerous other conventional and fluorescent staining methods exist, however, and include acridine orange, aniline-carbol-methyl violet and tartrazine, auramine O, auramine-rhodamine, auramine-carbol-fuchsin, 4',6-diamidino-2-phenylindole (DAPI), Giemsa, hemacolor, mepacrine, modified Kohn's, modified Koster, negative staining, safranine-methylene blue, propridium iodide, and others (Heine 1982; Current 1983; Payne et al. 1983; Baxby et al. 1984; Kageruka et al. 1984; Ma et al. 1984; Pohjola 1984; Casemore et al. 1985; Milácek and Vítovec 1985; Kawamoto et al. 1987; Asahi et al. 1988; Chermette and Boufassa-Ouzrout 1988; Arrowood and Sterling 1989; Chichino et al. 1991; Cozon et al. 1992; Ungureanu and Dontu 1992; Grimason et al. 1994; Kang and Mathan 1996). In these techniques, differentiation of species is accomplished based on knowing which *Cryptosporidium* sp. occurs in which host species and on the relative oocyst sizes (see above).

Immunofluorescent antibody (IFA) assays require the use of a primary monoclonal or polyclonal antibody directed against one or more epitopes on the outer oocyst wall, followed by some form of fluorescent detection. Although a number of variables, including aging of oocysts, storage and fixation media, and cross-reacting epitopes from contaminants can compound the assays, the IFA assay tends to be more specific and sensitive than staining fecal smears (Casemore et al. 1985; Sterling and Arrowood 1986; Stibbs and Ongerth 1986; Garcia et al. 1987, 1992; McLauchlin et al. 1987; Stetzenbach et al. 1988; Arrowood and Sterling 1989; J.B. Rose et al. 1989; Rusnak et al. 1989; Tsaihong and Ma 1990; MacPherson and McQueen 1993; Tee et al. 1993; Grigoriew et al. 1994; Rodríguez-Hernandez et al. 1994; Kehl et al. 1995; LeChevallier et al. 1995; Rodgers et al. 1995; Zimmerman and Needham 1995). Although most diagnostic tests have been developed specifically to detect *C. parvum,* several companies market tests that identify oocysts of multiple *Cryptosporidium* spp. (Garcia et al. 1987; Arrowood and Sterling 1989; J.B. Rose et al. 1989; Vesey et al. 1994; Graczyk et al. 1996a). None of the IFA assays are known to be entirely species specific.

A variety of commerically available EIAs are available for detection of *C. parvum* in feces. These have been shown repeatedly to be superior to acid-fast staining, but generally cannot be performed using routine laboratory reagents. Arrowood (1997) provides a summary of the sensitivity and specificities of five commercially available test kits that have been studied in peer reviewed journals. Several others have been examined since his chapter was written. Sensitivities range from 66% to 100% and specificities from 93% to 100% (Siddons et al. 1992; Newman et al. 1993; Rosenblatt and Sloan 1993; Aarnaes et al. 1994; Dagan et al. 1995; Kehl et al. 1995; McCluskey et al. 1995; Parisi and Tierno 1995; Zimmerman and Needham 1995; Graczyk et al. 1996a; Garcia and Shimizu 1997). Graczyk et al. (1996a) examined multiple *Cryptosporidium* spp. collected from mammals, birds, and reptiles and concluded that the EIA was less specific and less sensitive for non–*C. parvum* isolates than direct and indirect IFA-based tests. Again, none of these tests are species specific.

The techniques that are now gaining in popularity for typing *Cryptosporidium* spp. are molecular-based assays. PCR-based assays have the potential not only to detect the presence of single oocysts in samples, but also to determine the exact species of *Cryptosporidium* in question. DNA probes specific for *C. parvum* and several other *Cryptosporidium* spp. have been developed in many laboratories and include assays using both specific and random primers (Laxer et al. 1991, 1992; Johnson et al. 1993, 1995; Webster et al. 1993, 1996; Awad-El-Kariem et al. 1994; Filkorn et al. 1994; Morgan et al. 1995, 1996; Wagner-Wiening and Kimmig 1995; Balatbat et al. 1996; Laberge et al. 1996a; Leng et al. 1996; Mayer and Palmer 1996; Stinear et al. 1996; Gobet et al. 1997; Rochelle et al. 1997a,b). The main disadvantage of PCR-based diagnostic tests is that a certain degree of expertise as well as expensive reagents and equipment are currently required. In the near future, however, it appears that some versions will allow for rapid, colorimetric diagnosis of *Cryptosporidium* infections without the need for elaborate equipment or expertise.

Immunity. *Cryptosporidium parvum* appears to make little effort to evade the immune system of the host.

Many of the surface proteins, glycoproteins, and phospholipids are strongly immunogenic, and many surface molecules on both sporozoites and merozoites are antigenically cross-reactive. The success of the parasite appears to be in its ability to develop rapidly and flood the environment with oocysts. If this parasite were not efficiently eliminated from the body in a reasonable amount of time, it would soon kill many animals through dehydration and electrolyte imbalance, rapidly eliminating host species from the environment. Indeed, the severe effects of the parasite on immunosuppressed animals and humans clearly demonstrate the need for an effective immune response.

Cryptosporidiosis is primarily a disease of neonates. Although some adults become infected and shed low numbers of oocysts intermittently for long periods of time, clinical signs are generally absent except for unusual strains. Only in humans do adults commonly become acutely infected and have clinical disease, and this makes immunological studies difficult because of the lack of immunocompetent animal models. The mechanism by which age affects parasite development in the intestine is not yet known. However, this age-related susceptibility has been clearly documented (Mead et al. 1991; Novak and Sterling 1991; Harp et al. 1992; Kuhls et al. 1992; Harp and Sacco 1996; Upton and Gillock 1996), and Harp et al. (1992) suggested that this effect is mediated, in part, by the type of intestinal microflora. Upton and Gillock (1996) reported that developmentally expressed antigens may be the reason why neonates are more susceptible to infections than most adult animals.

Although infections with *C. parvum* generate an active humoral immune response, it is unclear whether these antibodies play a significant role in reducing the parasite burden. Antibody responses to both the 15–20 kDa antigen and 25–30 kDa antigen appear to be good indicators of infection (Mead et al. 1988; Hill et al. 1990; Répérant et al. 1992, 1994; Arnault et al. 1994; El-Shewy et al. 1994a,b; Moss et al. 1994; Ortega-Mora et al. 1994; Lorenzo et al. 1995; Tilley and Upton 1997), and both serum and mucosal antibodies generally are elevated at the time diarrhea and oocyst production wane (Tzipori and Campbell 1981; Lazo et al. 1986; Ungar and Nash 1986; Casemore 1987; Williams 1987; Mead et al. 1988; Hill et al. 1990; Whitmire and Harp 1991; Mosier et al. 1992; Peeters et al. 1992; Ortega-Mora et al. 1993). A number of studies also have shown that infected animals or individuals given antibodies orally often have lowered levels of infections, indicating a significant effect of antibody on parasite levels (Tzipori et al. 1986, 1987; Lopez et al. 1988; Arrowood et al. 1989; Fayer et al. 1989a,b, 1990; Bjorneby et al. 1990, 1991a; Nord et al. 1990; Ungar et al. 1990a; Cama and Sterling 1991; Perryman and Bjorneby 1991; Plettenberg et al. 1993; Watzl et al. 1993; Heaton 1994; Naciri et al. 1994; Riggs et al. 1994; Kuhls et al. 1995; Greenberg and Cello 1996). Nevertheless, there is no apparent correlation between exact serum or fecal antibody titers and elimination of the parasite, and numerous examples of individuals or animals with high anticryptosporidial antibody titers and persistent infections can be found (Ungar et al. 1986; Kassa et al. 1991; Kapel et al. 1993; Cozon et al. 1994; Benhamou et al. 1995; Favennec et al. 1995).

A variety of studies have demonstrated clearly the importance of CD4 cells, IFN-γ, IL-5, and IL-12 in the immune response (Ungar et al. 1990b, 1991; Gardner et al. 1991; McDonald et al. 1992, 1994; Chen et al. 1993a,b; Aguirre et al. 1994; Perryman et al. 1994; Gomez-Morales et al. 1995, 1996; Tilley et al. 1995; Huang et al. 1996; Urban et al. 1996; Riggs 1997; Wyatt et al. 1997). Studies involving major histocompatibility deficient class I (MHC class I) or class II (MHC class II) rodents have shown CD4 lymphocytes, but not CD8 lymphocytes, are required to prevent persistent infections (Aguirre et al. 1994). Alpha/beta-T-cells appear more important than γ/δ-T-cells in controlling the level of infection. Both neonate and adult αβ-T-cell–deficient mice develop persistent infections, whereas only γ/δ-T-cell–deficient neonates, not adults, develop slightly higher levels of infections over controls (Waters and Harp 1996). In immune calves, challenge infections result in a T-lymphocyte response favoring αβ-T-cells over γδ-T-cells (Abrahamsen et al. 1997).

Depletion of IFN-γ reduces prepatency, enhances oocyst output, and prolongs oocyst shedding in experimentally infected mice (Ungar et al. 1991; McDonald et al. 1992; Chen et al. 1993b; Kuhls et al. 1994; McDonald and Bancroft 1994; Tzipori et al. 1995; Urban et al. 1996). Depletion of IL-5, but apparently not IL-2 or IL-4, also significantly increases the level of infection (Ungar et al. 1991; Enriquez and Sterling 1993). Studies on activated intestinal T lymphocytes in calves have shown tumor necrosis factor alpha (TNF-α) to be elevated (Wyatt et al. 1997), but depletion of TNF-α in severe combined immunodeficiency disease (SCID) mice does not appear to increase susceptibility to infection (Chen et al. 1993a; McDonald et al. 1994).

Prevention and Control. Because all infections with *Cryptosporidium* spp. are initiated through ingestion of environmentally resistant oocysts, control of this stage is the single most important factor limiting the spread of cryptosporidiosis. As host density nearly always determines whether coccidial infections become epizootic, it is important to keep captive herd sizes sparse. The numbers and intensity of neonate calves infected with *C. parvum* have been shown to be proportional to herd size (Garber et al. 1994), and it is likely that a similar situation will be shown for other animals. Infected animals will contaminate the environment with oocysts; thus, animals producing detectable levels of oocysts should be isolated from uninfected cohorts to prevent spread of the disease. However, recent studies suggest many adult animals may periodically shed low numbers of oocysts into the environment, thus serving as reservoirs of the parasite (Villacorta et al. 1991;

Lorenzo-Lorenzo et al. 1993a; Xiao et al. 1993; Scott et al. 1995; Quílez et al. 1996; Tacal et al. 1987).

Animal husbandry, disinfection regimes, and hygiene are important factors that limit the spread of *Cryptosporidium.* In addition, animal handlers should be considered an important source of infection as they pass oocysts from enclosure to enclosure. Oocysts and feces containing oocysts will adhere to any surface, including skin, clothing, shoes, water bottles, feed, bedding, and tools. It is possible that insects, birds, or other animals that freely move between enclosures also carry infective oocysts mechanically. Wallace (1971, 1972) showed that both flies and cockroaches are capable of disseminating oocysts of *Toxoplasma gondii* in the environment, and both arthropods have been implicated in dissemination of *C. parvum* (Zerpa and Huicho 1994). Oocysts of *C. parvum* passing through the intestine of experimentally inoculated waterfowl remain viable and infective for laboratory rodents, even when feces are collected 6–7 days postinfection (Graczyk et al. 1996b, 1997). No reasonable technique will eliminate 100% of the viable oocysts or keep all animals from becoming infected. For instance, oocysts were still passed in the feces several days after calves were removed in plastic bags at birth to new stalls (Heine et al. 1984b). Cryptosporidiosis, however, can become a manageable disease.

Fayer et al. (1997) lists 26 commercially available disinfectants, employed by various investigators, that had little or no effect on parasite infectivity, even when *C. parvum* oocysts were exposed at intervals ranging from 30 minutes to 24 hours. At least some oocysts remain infective even after exposure to 15,000 mW/sec ultraviolet light for 2, but not 2.5, hours (Lorenzo-Lorenzo et al. 1993b); -15° C for 24 hours, but not 1 week (Fayer 1994); -20° C for 8, but not 24, hours (Fayer 1994); and +59.7° C for 5 minutes, but not +60° C for 6 minutes (Fayer and Nerad 1996). Typically, 100% of the encysted parasites are killed only when extreme and unpractical measures are employed. These include exposure to 1 J/cm^2 pulsed light (Dunn et al. 1995), 100% bromomethane gas for 24 hours (Fayer et al. 1996b), 28,000 mg/l chlorine for 24 hours (Smith et al. 1990), 10% formol saline for 18 hours (Campbell et al. 1982), 5% ammonia for 18 hours (Campbell et al. 1982), and 100% ethylene dioxide gas for 24 hours (Fayer et al. 1996b). Lengthy exposures to gaseous or aqueous solutions of ammonia, hydrogen peroxide, high concentrations of chlorine and related compounds, and short-term exposure to ozone significantly reduce numbers of viable *C. parvum* oocysts, but only rarely result in 100% efficacy (Fayer 1995; Fayer et al. 1997; Rose et al. 1997).

Perhaps the most effective and economic method to reduce the numbers of oocysts in the environment is desiccation. Using dye exclusion to measure viability, Robertson et al. (1992) found viability of a population of air-dried *C. parvum* oocysts to be reduced by 97% after 2 hours and 100% after 4 hours. Feces containing *C. parvum* oocysts that were air dried for 1 day were found to be noninfectious for suckling mice in another study (Anderson 1986). These data imply that application of aqueous disinfectant solutions, which keep feces moist, may result in prolonging parasite survival in feces rather than reducing parasite numbers.

Treatment. Dozens of compounds have undergone various in vivo evaluations for efficacy against *C. parvum* infections, and testing has included both rodent and, occasionally, ruminant animal models. Virtually all of the traditional anticoccidials and other antimicrobials consistently fail to eliminate infections entirely at nontoxic levels, although some reduce parasite numbers significantly. Blagburn and Soave (1997) provide an extensive list of in vivo drug trials against this parasite, and results suggest the most effective compounds to be ionophores (alborixin, halofuginone, lasalocid, and maduramicin), the aminoglycoside paromomycin, the nucleoside analog arprinocid, the macrolide azithromycin, the steroid dehydroepiandrosterone, the sulfonamide sulfadimethoxine, and the immune modulator diethyldithiocarbamate. In ruminants, paromomycin and the ionophores have received the greatest attention. In one experiment, calves fed 25–100 mg/kg body weight paromomycin in their milk twice daily for 11 consecutive days prior to oral inoculation had significantly fewer parasites in the feces and less diarrhea than unmedicated controls (Fayer and Ellis 1993). Mancassola et al. (1995) used paromomycin prophylactically in kid goats at 100 mg/kg body weight daily to delay and dramatically lower oocyst shedding in experimentally infected animals. In calves, Naciri et al. (1993) found halofuginone at concentrations of 60 and 120 µg/kg body weight daily delayed oocyst shedding and reduce signs of clinical disease in a dose-dependent manner. Halofuginone at 500 µg/kg body weight daily also was shown to reduce and delay oocyst shedding in experimentally infected lambs (Naciri and Yvoré 1989).

Because treatment regimes for *C. parvum* largely are ineffective, current therapy for severe cryptosporidiosis involves oral or parenteral rehydration using fluids and electrolytes. Although most reports involve humans or calves, Hovda et al. (1990) described success using parenteral therapy to reverse weight loss, electrolyte imbalance, and cachexia associated with prolonged diarrhea in a llama severely infected with *C. parvum.*

Public Health Concerns. Because so many mammalian species can be infected with *C. parvum,* a large potential zoonotic reservoir exists. Numerous studies have demonstrated or correlated transmission of the parasite from animals to humans, especially to children. These cases generally involve direct exposure to infected animals or their feces or exposure to contaminated raw milk, food, or water (Babb et al. 1982; Blagburn and Current 1983; Rahman et al. 1984; Casemore et al. 1986; Pohjola et al. 1986; Ribeiro and Palmer 1986; Biggs et al. 1987; Shahid et al. 1987; Hamoudi et al. 1988; Levine et al. 1988; Casemore 1989, 1990;

Palmer and Biffin 1990; Shield et al. 1990; Miron et al. 1991; Nouri and Karami 1991; Nouri and Toroghi 1991; Lengerich et al. 1993; Smith 1993; Millard et al. 1994; Nimri and Batchoun 1994; Sanchez-Mejorada and Ponce-de-Leon 1994; Dawson et al. 1995; Laberge et al. 1996b). One study suggested a case of airborne transmission (Højlyng et al. 1987).

Although wildlife may, at first, appear to be obvious sources of oocysts in surface waters, it is difficult to determine the degree to which wild animals actually contribute to overall numbers of infections. Ruminants, especially cattle, sometimes are implicated when high parasite numbers are detected (Ongerth and Stibbs 1987, 1989; J.B. Rose et al. 1988; Hansen and Ongreth 1991; Ong et al. 1996), but most studies fail to pinpoint the source of contamination. Ong et al. (1996) were able to correlate higher numbers of oocysts downstream from a cattle range with calving activity. Because cervids (above), beaver (Isaac-Renton et al. 1987), and rodents (above) are known to harbor the parasite and frequently are associated with watersheds, it is likely that at least some oocysts originate from these hosts in North America.

Domestic Animal Health Concerns. The role by which wildlife contribute to infections in domestic animals has not been elucidated. Occasional introduction of the parasite into domestic animal populations from wildlife such as deer, medium-sized mammals, or rodents probably occurs regularly. However, since the majority of information on prevalence of *C. parvum* worldwide demonstrates a high prevalence in cattle and other ruminants, it is likely that domestic animals themselves are responsible for most cases of domestic animal cryptosporidiosis.

Management Implications. Natural infections in wildlife with the various species of *Cryptosporidium,* especially *C. parvum,* will continue to occur despite the best of management practices. In some instances, severely infected animals probably can be removed from wild populations to reduce numbers of oocysts in a local area. This may be especially important in the spring when birthing occurs, although it is impractical under most conditions. However, as stated above, recent evidence has suggested that high numbers of adult animals continue to shed low numbers of oocysts into the environment, thus serving as reservoirs for neonates.

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